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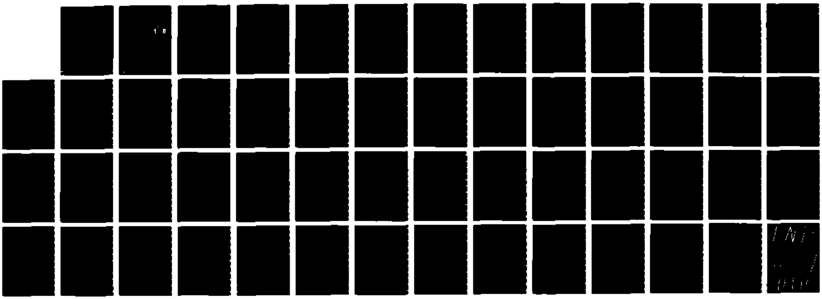

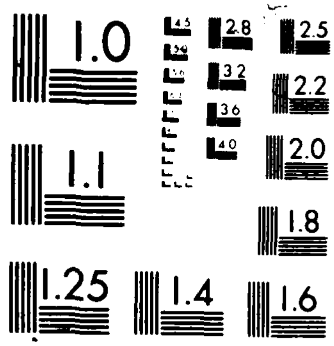

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SYNTHESIS OF NEW PROPHYLACTIC ANTIRADIATION DRUGS

ANNUAL AND FINAL REPORT

LUDWIG BAUER

AUGUST 1985

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

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University of Illinois at Chicago
Health Sciences Center
Chicago, Illinois 60680

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Synthesis of 2-mercaptoacetamidines from (1-aryl-2-adamantyl)alkylamines and (2-aryl-1-adamantyl) alkylamines

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Syntheses of (1-aryl-2-adamantyl)alkylamines and (2-aryl-1-adamantyl)alkylamines from 4-protoadamantanone are described. Conversion of these amines to the corresponding N-substituted 2-mercaptoacetamidines and derivatives is reported.

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Foreword:

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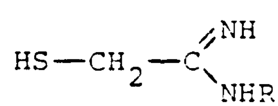
SYNTHESIS OF NEW PROPHYLACTIC ANTIRADIATION DRUGS

N-[(Aryl Substituted Adamantyl)alkyl] 2-Mercaptoacetamidines and Derivatives

A. Introduction

This Report summarizes the work carried out under Contract DAMD 17-79-C-9146 awarded September 30, 1979, and actually carried out between March 1, 1980 and August 31, 1985. This Report is a detailed account of the results of our investigations between August 1, 1984 and August 31, 1985. Details of all prior work can be found in Technical Reports which had been submitted previously.[1-5]

The overall objective for the past 5 years was to synthesize and submit for testing a series of 2-mercaptoacetamidines, 1, as potential prophylactic



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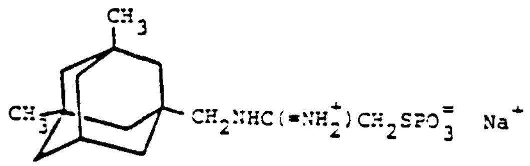
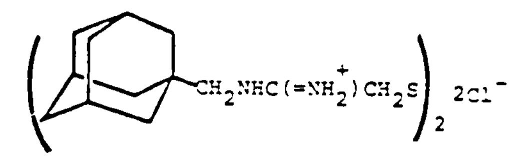
antiradiation drugs. In the ideal state, these drugs become active candidates if the following conditions were met: (1) a toxic dose is one which is considerably below the dose needed for radiation-protective activity; (2) protection was afforded to test animals if the compounds were administered orally at a relatively short period prior to exposure to otherwise lethal radiation; (3) that the animals had a relatively good survival ratio (compared to unprotected test animals) over preferably a period of a month, or so.

Some of the lead compounds for this project stemmed from work carried out previously on N-substituted 2-mercaptoacetamidines.[6,7] Two of the best compounds from prior work were the N-(adamantane)alkyl acetamidine derivatives, 2 and 3.[6,7]

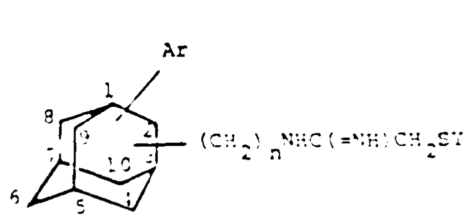


2 (WR-159,243)



3 (WR-155,419)

The compounds which have been prepared in the final phases of the Contract are those in which the substituent (**R**) was attached to one of the nitrogen atoms of the amidine in structure **1** and whose structure was closely defined, in following terms. The N-substituent should be an [(aryl substituted)-adamantane] alkyl group, as shown in the overall structure **4**. It was envisioned that the aromatic group, **Ar**, in **4** was to be quite diverse and that the alkyl side chain separating the adamantane ring from the amidine group be relatively short, preferably 1 to 3 carbon atoms. It was originally intended to keep the aromatic ring and the amidino group relatively close to each other. The sulfur-bearing groups, **SY** in **4** were in this order of preference: thiol (SH), phosphorothioate (SPO_3H_2), or disulfide (-S-S-).



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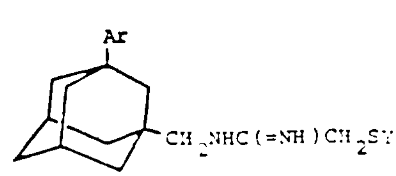

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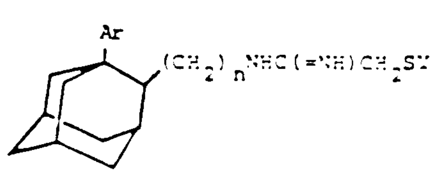
It was of interest to ascertain the radiation-protective properties of a number of pairs of isomeric compounds in this series. It was hoped that some parameters might be established to provide clues on structural requirements for relatively low toxicity and comparatively good activity in this series of compounds.

In the earlier phases of the work,[4,5] a considerable amount of work was expended on the synthesis of a number of 1,3-disubstituted adamantane derivatives, which are best summarized by structure **5**. The aromatic moieties in **5** consisted of the following groups: 4-fluorophenyl, 4-methylthiophenyl, 4-tolyl, 4-anisyl, and 2-thienyl; the sulfur-bearing groups, SY, were either a thiol, or disulfide, or Bunte salt or phosphorothioate. The scope of these investigations are best illustrated by including Table I and II which show the biological activity[5] and Table III which summarizes the concluding phases of this work. The majority of this earlier investigation was completed by the summer of 1984.[5]

The contents of this Report describe the syntheses of a number of 1,2-disubstituted adamantane derivatives, the substituents, in which an aryl group and an appropriate aliphatic side chain are attached to vicinal carbons of the adamantane ring. The mercaptoamidino groups are part of the side chain. The most general structures representing two plausible arrangements are shown in structures **6** and **7**, where SY stands for a divalent sulfur functional group, such as a mercaptan (-SH), disulfide (-S-S-) or phosphorothioate ($-SPO_3H_2$).



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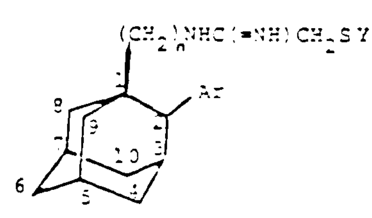

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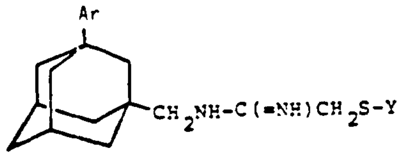
Table I: Summary of Acute Toxicity Studies in Mice (IP Administration)



WR-No	Ar	Y	Mol. Formula (Mol. Weight)	Vehicle	Dose* mg/kg	Deaths	30-Day Survivors, %	LD_{50} (10 days)
249,914	4-methyl-phenyl	PO_3HNa	$C_{20}H_{28}N_2O_3PSNa$	Saline	120.0	5/5	0	
			(430.47)		60.0	3/5	40	
					30.0	0/5	100	
					15.0	0/5	100	60
249,915	4-methyl-phenyl	disulfide	$C_{40}H_{56}Cl_2N_4S_2$	Water-	60.0	5/5	0	
		(2 HCl)	(727.97)	10% Tween 80	30.0	5/5	0	
					15.0	4/5	20	
					7.5	0/5	100	10
249,939	4-methyl-phenyl	SO_3H	$C_{20}H_{28}N_2O_3S_2$	20% EtOH-	600.0	5/5	0	
			(408.58)	Tween 80	300.0	5/5	0	
					150.0	5/5	0	
					75.0	5/5	0	
					37.5	5/5	0	
					18.75	3/5	40	
					9.38	0/5	100	19
250,021	4-methoxy-phenyl	disulfide	$C_{40}H_{56}Cl_2N_4O_2S_2$	20% EtOH-	600.0	4/5	20	
		(2 HCl)	(759.97)	Tween 80	30.0	5/5	0	
					15.0	0/5	100	
					7.5	0/5	100	20
250,022	4-methoxy-phenyl	PO_3HNa	$C_{20}H_{28}N_2O_4PSNa$	20% EtOH-	120.0	5/5	100	
			(446.47)	80% Water	60.0	0/5	0	
					30.0	0/5	0	
					15.0	0/5	0	90
250,023	4-methoxy-phenyl	H	$C_{20}H_{29}ClN_2OS$	10% EtOH-	600.0	5/5	0	
		(HCl)	(380.97)	Tween 80	300.0	5/5	0	
					150.0	5/5	0	
					75.0	5/5	0	
					37.5	5/5	0	
					18.75	3/5	40	
					9.38	0/5	100	35
250,083	4-fluoro-phenyl	PO_3HNa	$C_{19}H_{25}FN_2O_3PSNa$	20% EtOH	300.0	5/5	0	
			(434.44)		150.0	5/5	0	
					75.0	5/5		
					37.5	1/5	80	
					18.75	0/5	100	35
250,084	4-fluoro-phenyl	disulfide	$C_{38}H_{50}F_2Cl_2N_4S_2$	20% EtOH	300.0	4/5	20	
		(2 HCl)	(735.89)		150.0	5/5	0	
					175.0	4/5	20	
					37.5	1/5	80	
					18.75	0/5	100	55
50,281	4-(methyl-thio)phenyl	SO_3H	$C_{20}H_{28}N_2O_3S_3$	20% DMSO-	120.0	3/5	40	
			(440.64)	80% Water	60.0	1/5	80	
					30.0	0/5	100	
					15.0	0/5	100	
				Klucel	120.0	1/5	80	
					60.0	0/5	100	
					30.0	0/5	100	120

Table I Continued: Summary of Acute Toxicity Studies in Mice (IP Administration)

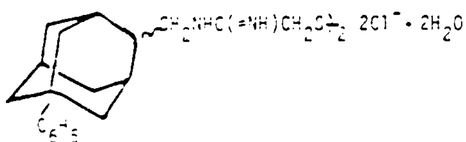
WR-No	Ar	Y	Mol. Formula (Mol. Weight)	Vehicle	Dose* mg/kg	Deaths	30-Day Survivors, %	LD_{50} (10 days)
205,282	4-(methyl-thio)phenyl	PO_3HNa	$C_{20}H_{28}N_2O_3S_2PNa$ (462.54)	20% EtOH- 20% Emulphor 60% Saline	102.0	5/5	0	
					51.0	0/5	100	
					25.5	0/5	100	
					12.75	0/5	100	76
205,393	2-thienyl	H (HCl)	$C_{17}H_{25}ClN_2S_2$ (356.98)	20% EtOH- 80% Water	600.0	5/5	0	
					300.0	5/5	0	
					150.0	5/5	0	
					75.0	5/5	0	
					37.5	5/5	0	37.5
205,394	for structure see below**	disulfide (2 HCl)	$C_{38}H_{52}Cl_2N_4S_2$ (699.90)	20% EtOH- 80% Water	600.0	5/5	0	
					300.0	5/5	0	
					150.0	5/5	0	
					75.0	0/5	100	112
251,794	for structure see below***	disulfide (2 HCl)	$C_{40}H_{56}Cl_2N_4S_2$ (727 97)	Klucel	75.0	5/5	0	
					37.5	5/5	0	
					18.75	5/5	0	
					9.37	3/5	60	
					4.69	0/5	100	
251,795	for structure see below****	disulfide (2 HCl)	$C_{38}H_{52}Cl_2N_4S_2$ (699.90)	Klucel	75.0	5/5	0	
					37.5	5/50		
					18.75	5/5	0	
					9.38	0/5	100	
					4.69	0/5	100	
249,319	for structure see below*****	SO_3H	$C_{18}H_{32}N_4S_4O_6$ (528.75)	Klucel	100.0	4/5	20	
					60.0	0/5	0	
					36.0	0/5	0	
					21.6	0/5	0	85

*Drug dosage is expressed in mg/kg and is corrected for salt and water content.

**Structure is: $[4\text{-}(1\text{-Adm})C_6H_4CH_2NH\text{-}C(=NH)CH_2S]_2$ 2 HCl, where 1-Adm is 1-adamantyl.

***Structure is: $[4\text{-}(1\text{-Adm})C_6H_4CH_2CH_2NHC(=NH)CH_2S\text{-}]_2$ 2 Cl^- where 1-Adm is 1-adamantyl.

****Structure is:



*****Structure is:

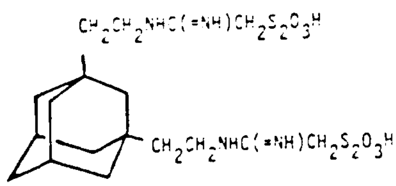
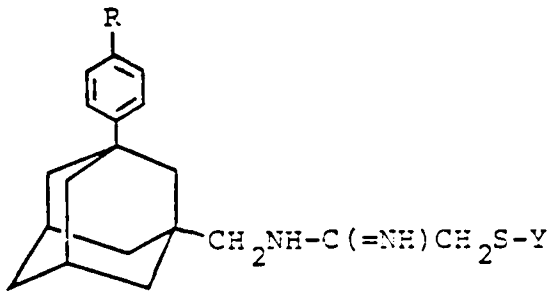


Table II: Radioprotectant Activity in Mice



WR-No	R	Y	Route	Drug Dose mg/kg*	Drug Related Lethality	30 Day Survivors, %**
249,914	CH_3	PO_3HNa	IP	30.0	1/10	40
				15.0	0/10	70
				7.5	0/10	30
				0.00	0/20	10
			IP	37.5	0/10	60
				18.75	0/10	50
				9.38	0/10	0
				4.69	0/10	0
				0.00	0/20	0
249,915	CH_3	disulfide (HCl)	IP	30.0	10/10	0
				15.0	6/10	10
				7.5	0/10	20
				0.00	0/20	10
			IP	9.38	1/10	80
				4.69	0/10	70
				2.35	0/10	20
				0.00	0/20	0
249,939	CH_3	SO_3H	IP	16.0	6/10	30
				8.0	0/10	80
				4.0	0/10	10
				2.0	0/10	30
				0.0	0/20	0
			PO	300.0	1/10	0
				150.0	0/10	0
				75.0	0/10	0
				0.0	0/20	0

Table II Continued: Radioprotectant Activity in Mice

WR-No	R	Y	Route	Drug Dose mg/kg*	Drug Related Lethality	30 Day Survivors, %**
250,021	OCH_3	disulfide (2 HCl)	IP	60.0	8/10	10
				30.0	10/10	0
				15.0	0/10	90
				7.5	0/10	20
				0.0	0/20	0
			PO	1200.0	1/10	0
				600.0	1/10	0
				300.0	0/10	0
				0.0	0/20	0
250,022	OCH_3	PO_3HNa	IP	60.0	7/10	20
				30.0	0/10	60
				15.0	0/10	30
				7.5	0/10	0
				0.0	0/20	0
			PO	600.0	6/10	10
				300.0	0/10	10
				150.0	1/10	30
				0.0	0/20	0
250,023	OCH_3	H (HCl)	IP	16.0	0/10	50
				8.0	0/10	30
				4.0	0/10	0
				2.0	0/10	0
				0.0	0/20	0
250,083	F	PO_3HNa	IP	36.0	6/10	40
				18.0	0/10	60
				9.0	0/0	80
				0.0	0/20	0
			IP	18.75	0/10	100
				9.38	0/10	40
				4.69	0/10	10
				0.00	0/20	0
			PO	150.0	0/10	40
				75.0	0/10	10
				37.5	0/10	20
				18.75	0/10	0

Table II Continued: Radioprotectant Activity in Mice

WR-No	R	Y	Route	Drug Dose mg/kg*	Drug Related Lethality	30 Day Survivors, %**
250,084	F	disulfide (2 HCl)	IP	36.0	10/10	0
				18.0	8/10	20
				9.0	0/10	80
				0.0	0/20	0
			IP	9.38	0/10	70
				4.69	0/10	40
				2.35	0/10	10
				0.00	0/10	0
			PO	300.0	0/10	0
				150.0	0/10	0
				75.0	0/10	0
				37.5	0/10	10
250,281	SCH_3	SO_3H	IP	60.0	1/10	50
				30.0	0/10	60
				15.0	0/10	60
				0.0	0/20	15
			IP	75.0	3/10	0
				37.5	0/10	0
				18.25	0/10	0
				9.38	0/10	0
				0.0	0/20	0
250,082	SCH_3	PO_3HNa	IP	60.0	1/10	70
				30.0	0/10	70
				15.0	0/10	30
				0.0	0/10	15
			IP	75.0	10/10	0
				37.5	0/10	40
				18.75	0/10	50
				4.38	0/10	0
				0.0	0/20	0

Table II Continued: Radioprotectant Activity in Mice

WR-No	R	Y	Route	Drug Dose mg/kg*	Drug Related Lethality	30 Day Survivors, %**
250,393	2-thienyl	H (HCl)	IP	20.0	0/10	60
				10.0	0/10	60
				5.0	0/10	0
				0.0	0/20	0
			PO	300.0	4/10	50
				150.0	0/10	60
				75.0	1/10	20
				37.5	0/10	0
				0.0	0/20	0
250,394	for structure see below***	disulfide (2 HCl)	IP	80.0	1/10	60
				40.0	0/10	0
				20.0	0/10	20
				0.0	0/20	0
249,319	for structure see below****	SO_3H	IP	75.0	9/10	0
				37.5	2/10	10
				18.75	0/10	0
				0.0	0/10	0

*Drug doses expressed as mg/kg corrected for salt and/or water content (see Table I for Molecular Formula) and were administered ip 30 minutes prior to radiation; see Table I for vehicle.

**Percent of mice surviving at 30 days after treatment with drug and whole-body irradiation of 1000 rads ($LD_{100/30}$).

***Structure is: $[4\text{-}(1\text{-Adm})C_6H_4CH_2NHC(=NH)CH_2\text{-}S]_2 \cdot 2\ HCl$.

****Structure is:

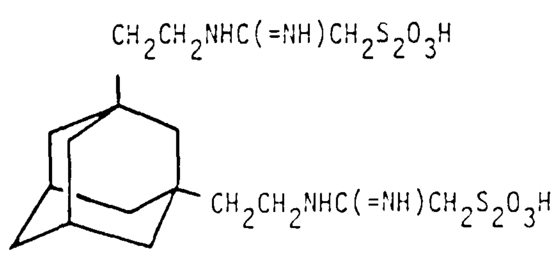
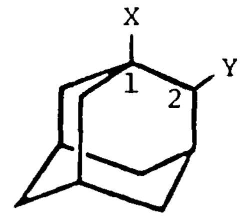
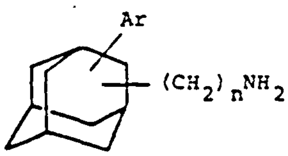


Table III: Summary of Compounds Submitted and Biological Data of 1,2-Disubstituted Adamantanes



					Toxicity Studies					Radio Protection			
[illegible] No.	WR-No	Substituent X	Substituent Y	Mol. Formula	Vehicle (Route)	Dose mg/kg	Toxic Deaths	% Mortality	LD_{50} (10 Days)	Route	Dose mg/kg	Toxic Deaths	% Survival
[illegible] 105 20	253,754	C_6H_5	$CH_2NHC(=NH)CH_2SPO_3H_2$	$C_{19}H_{27}N_2O_3PS$	Klucel (IP)	75 37.5 18.75	3/5 0/5 0/5	60 0 0	60	IP	37.5 18.75 9.38 0	0/10 0/10 0/10 0/10	90 60 20 0
[illegible] 63 19	253,567	C_6H_5	$(CH_2)_2NHC(=NH)CH_2SH.HCl$	$C_{20}H_{28}N_2S.HCl$	20% EtOH (IP)	18.75 9.375 4.688	5/5 0/5 0/5	100 0 0	14	IP	9.375 4.688 2.344 0	0/10 0/10 0/10 0/10	80 30 0 0
[illegible]6	254,593	$(CH_2)_2NHC(=NH)CH_2SPO_3H_2$	C_6H_5	$C_{20}H_{29}N_2O_3PS$	20% EtOH (IP)	740.7 370.4 185.2	5/5 5/5 4/5	100 100 80	150				
[illegible]7		$(CH_2)_2NHC(=NH)CH_2SH.HCl$	C_6H_5	$C_{20}H_{28}N_2S$									
[illegible] 115 20	253,97801	$4\text{-}CH_3OC_6H_4$	$(CH_2)_2NHC(=NH)CH_2SPO_3H_2$	$C_{21}H_{33}N_2O_4PS$									
[illegible] 19	254,35301	$4\ FC_6H_4$	$(CH_2)_2NHC(=NH)CH_2SPO_3H_2$	$C_{20}H_{28}N_2O_3PSF$									
[illegible] 166 25	254,76200	$4\ CH_3SC_6H_4$	$CH_2NHC(=NH)CH_2SPO_3H_2$	$C_{21}H_{31}N_2O_3S_2P$									

The first task on hand was to procure the necessary amines of general structure, **8**. A major portion of this report describes the synthesis of a number of amines belonging to the required 1,2-disubstituted adamantanes, types **9** and **10**.



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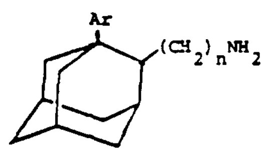

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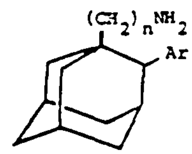


10

B. **Conversions of Amines to 2-Mercaptoacetamidines and Derivatives Thereof**

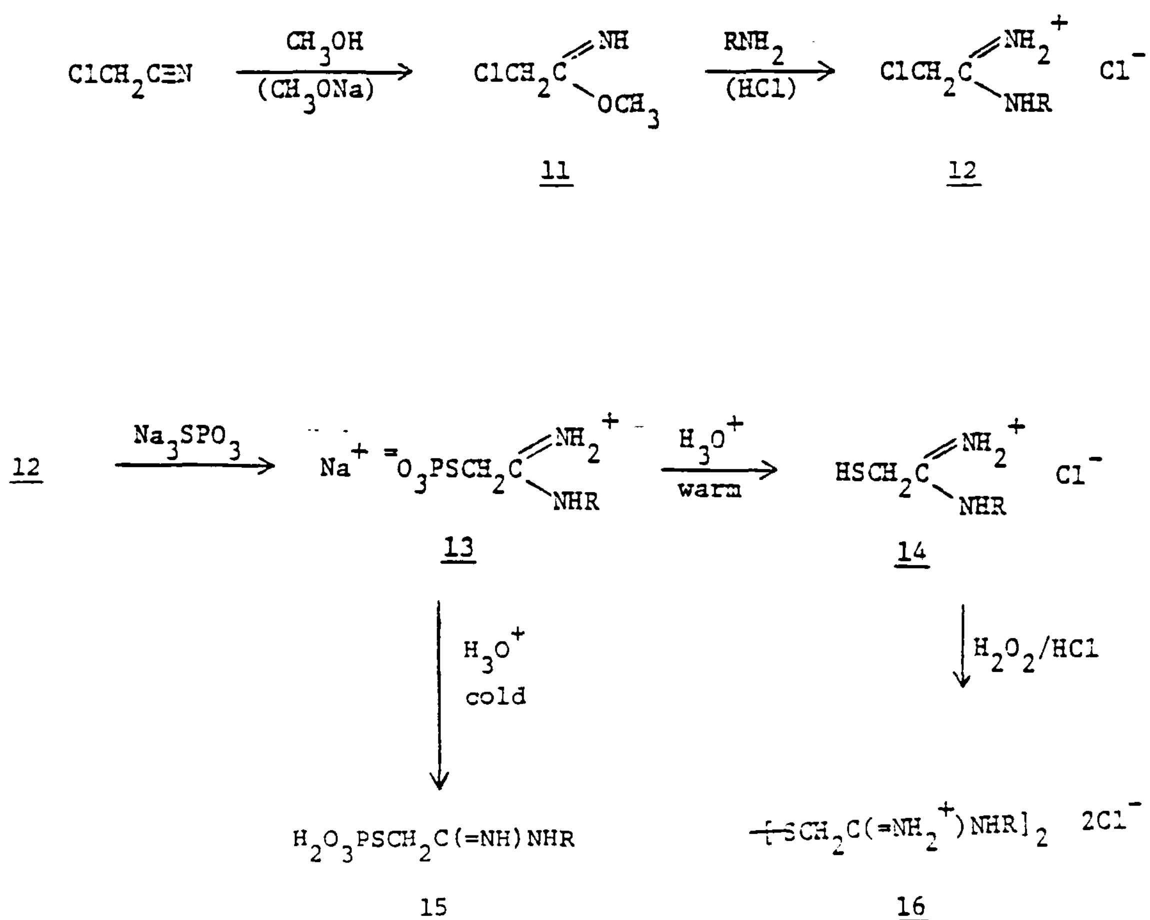
The major routes by which an amine, RNH_2, is converted to a 2-mercaptoamidine (**1**), which is usually isolated and handled as the hydrochloride, **4**, are summarized in **CHART I.**

Ethyl chloroacetimidate (**11**) generated by the base-catalyzed addition of methanol to chloroacetonitrile, $ClCH_2CN$, is reacted with an amine, RNH_2 in the presence of anhydrous HCl to form the appropriately N-substituted 2-chloroacetamidine hydrochloride, **12**. These chloro-amidine hydrochlorides were solids which could be purified before using in the next step.

The reaction of 2-chloroacetamidine hydrochlorides, **12**, with trisodium phosphorothioate produced some very insoluble amidinium phosphorothioates (**13**) in this series. Two ionic charges of the phosphorothioate group had to be neutralized by the amidinium ion and another cation. In prior experiments, the amidinium phosphorothioates were frequently isolated as sodium salts, **13**.

Chart I

Synthesis of 2-Mercaptoacetamidines and Related Phosphorothioates and Carboxamidinemethyl Disulfides



However, in the synthesis of recent members of this series, it was found that careful neutralization of **13** at low temperatures formed highly crystalline amidinium phosphorothiates, **15** (not shown in the zwitterionic form). We had originally avoided rendering the reaction mixture containing **13** too acidic, after the reaction **12** with Na_3SPO_3 to avoid potential hydrolysis of the phosphorothioate. But these zwitterionic salts, **13**, were so insoluble that they did not begin to hydrolyze upon standing some time at low temperatures in the acid medium. However, when **13** was warmed with HCl, hydrolysis took place to form the amidine mercaptan, **14**. Oxidation of the mercaptan afforded the disulfide, **16**.

The purity of all compounds was checked routinely by analyzing their proton NMR spectra. We were concerned about possible contamination of the phosphorothioates (**15**) by the corresponding mercaptan (**14**). Therefore samples of **15** were checked carefully by examining the requisite proton NMR spectra. In DMSO, the phosphorothioates, as well as the corresponding mercaptans had characteristics ^1H chemical shifts for the methylene protons attached to the sulfur function: for $CH_2SPO_3H_2$, there appeared a doublet around 3.40 ppm in DMSO-d_6 with a coupling of the order of 15.0 Hz (due to long-range proton-phosphorus coupling H-C-S-P). Although the chemical shift and the size of this long-range coupling was slightly sensitive to changes in solvent, under no circumstances could this doublet be collapsed by the addition of D_2O. This is in contrast to the resonance for $C\underline{H}_2$-SH appeared as a singlet around 3.35 ppm in DMSO-$\underline{d}_6$. Had there been visible coupling between the methylene and thiol protons (-CH_2-SH), a doublet would collapse to a singlet upon addition of D_2O in DMSO-$\underline{d}_6$. Therefore, it was always easy to examine **15** or potential impurities of **14**. Furthermore, any contamination of **15** by the corresponding

disulfide, **16**, would also have been noticed, since in DMSO-$\underline{d}_6$, the CH_2-S-S- signals appear as a singlet around 3.60-4.00 ppm.

The two spectra which are attached, Figures 1 and 2, are indicative of where pertinent methylene proton resonances are formed and attest to the purity of the compounds involved through their general appearance, appropriate chemical shifts and correct integration.

C. Syntheses of (1-Aryl-2-adamantyl)alkylamines and 2-Mercaptoacetamidine Derivatives (See, CHART II)

General methods for the synthesis of 1-aryl-2-(ω-aminoalkyl)adamantanes (**9**) were developed. These amines were required for the synthesis of the target N-substituted 2-mercaptoacetamidines, as outlined in Section B.

A common precursor for the synthesis of 1-aryl-2-(ω-aminoalkyl)adamantanes is an 1-aryl 2-adamantanone, **24**. Once the ketone becomes available, the alkyl side chain can be introduced in a variety of ways. The synthesis of these ketones followed the route which we had developed and is the one outlined in **CHART II.**

1-Bromoadamantanone (**17**) was hydrolyzed to 1-adamantanol (**18**) in excellent yield by the modification of the literature method.[8] The usual method calls for the hydrolysis with dil. HCl in hot DMF. Occasionally, starting bromide coprecipitates with 1-adamantol. It is advisable to dissolve **17** in hot DMF and add the dil. HCl dropwise at that temperature. Oxidative cleavage of **18** with iodine and lead tetraacetate formed the iodo ketone, **19**, which was not isolated but was cyclized immediately in a basic medium to form 4-protoadamantanone (**20**).[9] Addition of a Grignard reagent from the requisite aryl halide produced a mixture of the endo and exo-alcohols (**21**)[10] which were not separated or purified.

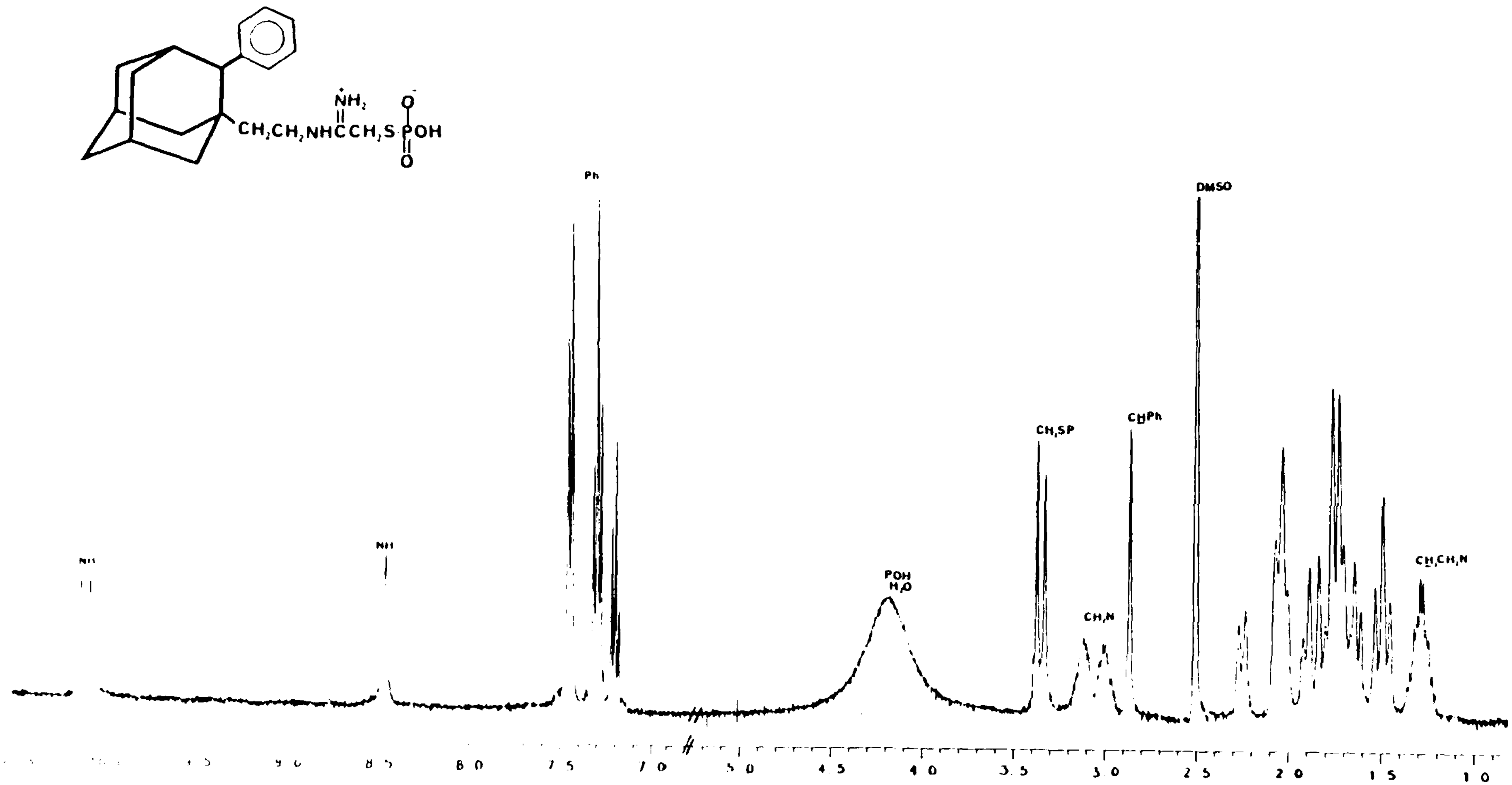


Figure 1. ^1H NMR Spectrum of 42 (360 MHz, DMSO-d_6).

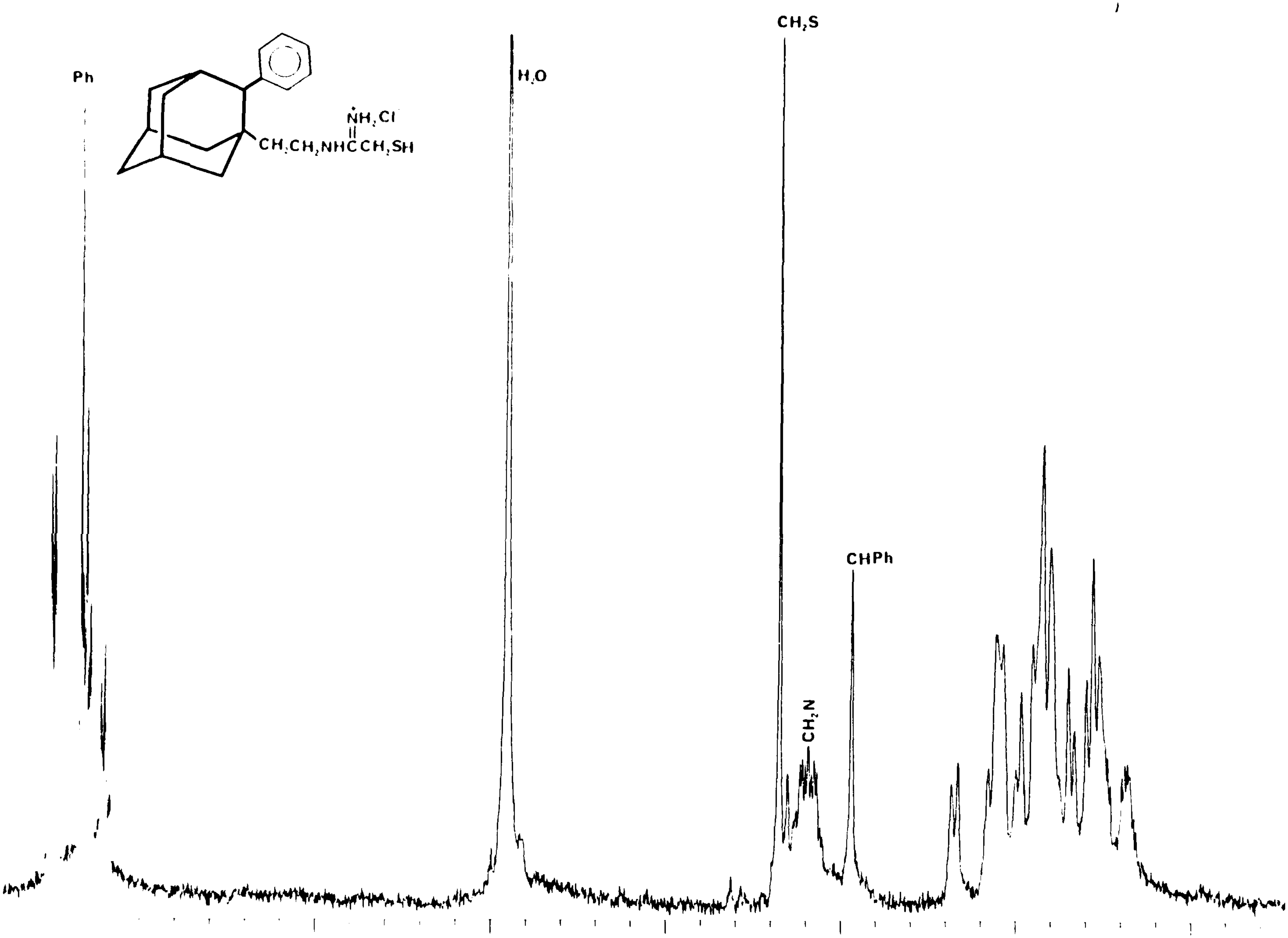
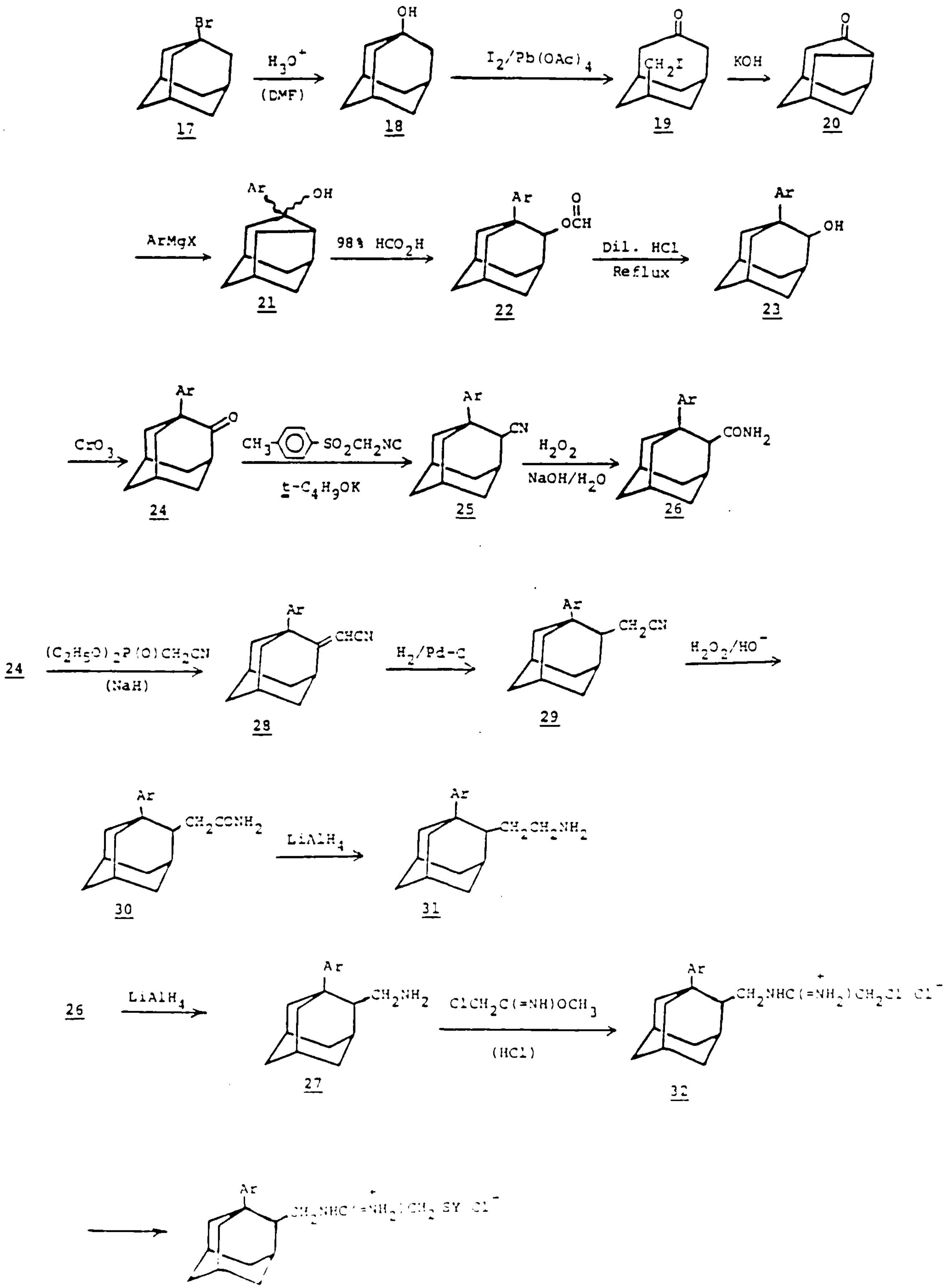


Figure 2. ^{1}H NMR Spectrum of <u>43</u> (360 MHz, CD_3OD).

CHART II



Br
H_3O^+
(DMF)
OH
$I_2/Pb(OAc)_4$
O
CH_2I
KOH
O
17
18
19
20
ArMgX
Ar
OH
98% HCO_2H
Ar
O
OCH
Dil. HCl
Reflux
Ar
OH
21
22
23
CrO_3
Ar
O
CH_3-⟨⟩-SO_2CH_2NC
t-C_4H_9OK
Ar
CN
H_2O_2
$NaOH/H_2O$
Ar
$CONH_2$
24
25
26
24
$(C_2H_5O)_2P(O)CH_2CN$
(NaH)
Ar
CHCN
H_2/Pd-C
Ar
CH_2CN
H_2O_2/HO^-
28
29
Ar
CH_2CONH_2
$LiAlH_4$
Ar
$CH_2CH_2NH_2$
30
31
26
$LiAlH_4$
Ar
CH_2NH_2
$ClCH_2C(=NH)OCH_3$
(HCl)
Ar
$CH_2NHC(=\overset{+}{N}H_2)CH_2Cl\ Cl^-$
27
32
Ar
$CH_2NHC(=\overset{+}{N}H_2)CH_2SY\ Cl^-$

Rearrangement of **21** with 98% formic acid led to 1-aryl-2-formyloxyadamantanes, **22.**[10] These esters were hydrolyzed to 1-aryl-2-adamantanols, **23.** This general method was applied to the synthesis of alcohols, **23,** in which Ar was phenyl, 4-fluorophenyl, 4-methoxyphenyl and 4-methylthiophenyl.

Jones oxidation of the alcohols (**23**) proceeded well to form the ketones, **24.** An exception was of course the 4-methylthiophenyl alcohol. Due to the susceptibility of the sulfide towards such oxidation, alternate methods were sought for this oxidation. The method which was adapted and worked well was the dimethyl sulfoxide-acetic anhydride oxidation[11] and the ketone **24** (Ar = 4-$CH_3SC_6H_4$) was obtained in 96% yield.

Since our efforts concentrated initially on the attachment of an 1 or 2-carbon atom side chain, we concentrated on just several major methods to achieve this goal.

To introduce an one-carbon side chain, the ketones (**24**), were converted to the corresponding nitriles by using the van Leusen reagent,[12] 4-toluenesulfonylmethylisocyanide (TOSMIC) and potassium t-butoxide. The reaction was monitored by TLC to permit it to go to completion. Due to some hindrance at C-2, the reaction took a little longer to complete than recommended for less hindered ketones. But, the yields of **25** were excellent.

The nitriles (**25**) were converted to an aminomethyl group in one of two ways. Although direct catalytic reduction or lithium aluminum hydride reduction, seemed to be an obvious way to go, these reactions were fraught with all kinds of problems. A more reliable route was to convert the nitrile with basic hydrogen peroxide[13] to the corresponding amide, **26**, which, in turn, was reduced by $LiAlH_4$ to the required amine without any problem. We found that sometimes the direct reduction of the nitrile to the amine worked when

sodium borohydride and cobaltous chloride (equivalent to cobalt II hydride) was used as the reducing agent.[14]

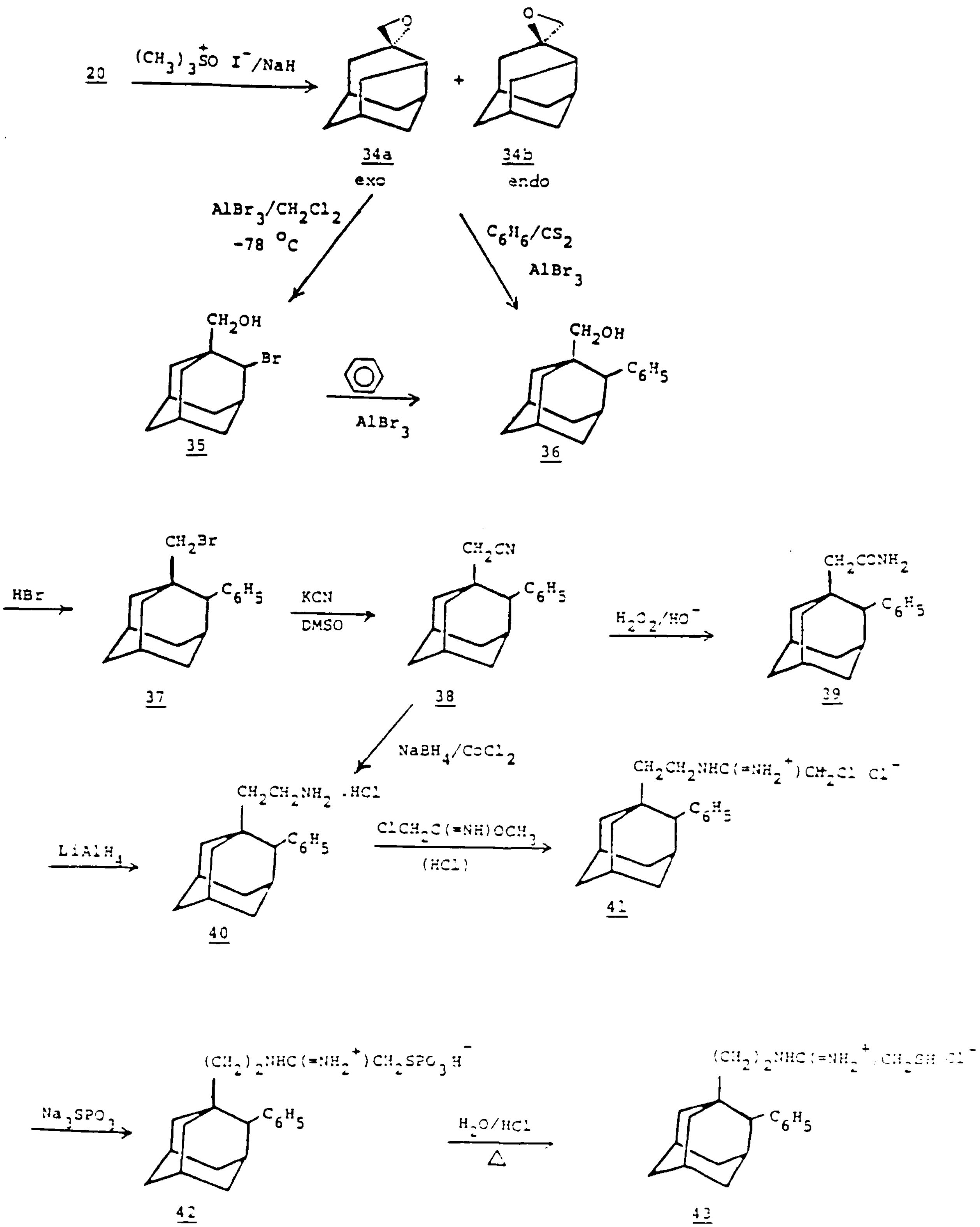
To convert the ketones **24**, to a 2-aminoethyl side chain, the following route proved to be quite reliable. A Wittig (Horner-Emmons modification) reaction on the ketone with diethyl cyanomethylphosphonate and sodium hydride converted **24** to a cyanovinyl compound, **28**. Preferential catalytic reduction of the alkene was very clean and yielded the saturated nitriles, **29**, in excellent yield. The problems associated with the reduction of these nitriles were quite similar for those discussed for the reduction of nitriles, **25**. The best and most reliable method was to go through the corresponding amides, **30**. At reduction of **30** afforded the amines **31**, which were usually isolated and handled best as their hydrochlorides.

These amines were converted by the route outlined in **CHART I** first to the 2-chloroacetamidine hydrochloride, **32**, and then to the 2-mercaptoacetamidine or derivative, **33**.

D. Synthesis of 1-Amino-2-(2-phenyl-1-adamantyl)ethane and 2-Mercaptoacetamidine Derivatives (See, CHART III)

A general method was developed for the synthesis of 1,2-disubstituted adamantanes bearing an aryl group at C-2 and a 2-aminoethyl side chain on C-1. It also started from 4-protoadamantanone, **20.**[9] Reaction of this ketone with trimethylsulfoxonium iodide and sodium hydride formed a mixture of the endo and exo epoxides, **34.**[15,16] The reaction of these epoxides with $AlBr_3$ in methylene chloride at -78°C provided 1-hydroxymethyl-2-bromoadamantane (**35**) in excellent yield. This bromide underwent a Friedel-Crafts reaction with benzene which provided 1-hydroxymethyl-2-phenyladamantane (**36**). Attempts to extend the Friedel-Crafts reactions of **35** with toluene produced a tolyl

CHART III


20
$(CH_3)_3\overset{+}{S}O\ I^-/NaH$
34a
exo
34b
endo
$AlBr_3/CH_2Cl_2$
-78 °C
C_6H_6/CS_2
$AlBr_3$
CH_2OH
Br
35
$AlBr_3$
CH_2OH
C_6H_5
36
HBr
CH_2Br
C_6H_5
37
KCN
DMSO
CH_2CN
C_6H_5
38
H_2O_2/HO^-
CH_2CONH_2
C_6H_5
39
$NaBH_4/CoCl_2$
LiAlH$_4$
$CH_2CH_2NH_2\cdot HCl$
C_6H_5
40
$ClCH_2C(=NH)OCH_3$
(HCl)
$CH_2CH_2NHC(=NH_2^+)CH_2Cl\ Cl^-$
C_6H_5
41
Na_3SPO_3
$(CH_2)_2NHC(=NH_2^+)CH_2SPO_3H^-$
C_6H_5
42
H_2O/HCl
Δ
$(CH_2)_2NHC(=NH_2^+)CH_2SH\ Cl^-$
C_6H_5
43

analog of **36**, which was however contaminated by either or both of the ortho and meta isomers. Since Friedel-Crafts reactions with substituted benzenes frequently give mixtures of isomers, this approach was abandoned. However, the synthetic sequence was worked but starting from the phenyl compound, **36.**

To convert the aliphatic side chain of **36** the appropriate amine, the following reactions were carried out. Boiling 48% HBr converted **36** to the bromide, **37.** A nucleophilic displacement reaction with cyanide ion yielded the nitrile, **38** which was converted to the amide **39** which was reduced by $LiAlH_4$ to the amine **40.** Alternatively, **38** was directly reduced with sodium borohydride in the presence of cobaltous chloride to form the amine, **40.** The amine was handled as the hydrochloride.

The amine, **40**, was converted first to the chloro amidine hydrochloride, **41**, then to the phosphorothioate, **42**, and finally to the mercaptoacetamidine **43.** There are several comments regards some of these steps, to insure their success. It is best to have the amine (**40**) as pure as possible, usually as the hydrochloride. The chloroamidine hydrochloride (**41**) is best purified to a high degree since the phosphorothioates (**42**) are frequently gummy and tak quite some time to crystallize. Also, the fewer steps required to purify **42** is preferred. Some of these amidinium phosphorothioates are virtually insoluble in most solvents, or decompose upon extensive heating. Purities of **41** must be checked along the purification steps, preferably by ^1H NMR.

E. Experimental Section

1. General Methodology

Melting points were determined on a Thomas Hoover Unimelt capillary melting point apparatus and are uncorrected. Microanalyses were carried out by Micro-Tech Labs, Skokie, IL. Infrared (IR) spectra were recorded on a FT-IR spectrometer, Model MX-1, Nicolet Instrument Corporation. Proton (^1H) NMR spectra were recorded in $CDCl_3$ or DMSO-$\underline{d}_6$ on a T60A Varian spectrometer fitted with a Nicolet TT-7 Fourier transform accessory operating at 60 MHz or on Nicolet NIC-360 spectrometer operating at 360 MHz, respectively. ^{13}C NMR spectra were obtained on the NIC-360 instrument operating at 90 MHz for carbon and using a 5 mm probe. All chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane and signals are designated as singlets (s), doublets (d), doublet of doublets (dd), triplets (t), quartets (q), multiplets (m). Mass spectra (MS) were obtained at 70 eV by Mr. Richard Dvorak using a Varian MAT 112 S mass spectrometer. In general, ions with intensities of 20% or more for the base peak are reported (unless deemed important) and relative intensities are shown in parentheses.

Gas chromatograms were obtained on a Varian Aerograph 2740 instrument using a 3% SE-30 on 100/120 mesh Veraport-30 5 ft x 1/8 in column. Temperature programming (150 ^{o}C to 250 ^{o}C at a rate of 10 ^{o}C/min) was used unless otherwise stated and helium was the carrier gas.

Gas chromatography/mass spectrometry (GC/MS) was done on a Finnigan MAT 4510 instrument or a Varian MAT 112S using a DB-1 30 m x 0.32 mm i.d. (film thickness 0.25 m) or a SE-54, or a DB-5 30 m x 0.25 mm id fused silica capillary columns with He as a carrier gas (flow rate 2 mL/min, injector temperature 280 ^{o}C, split ratio 2:35). Temperature programming (150-300 ^{o}C

at a rate of 10^{o}/min) was used, unless otherwise stated. Mass spectra were scanned at a rate of 1 or 2 sec/dec at an ionizing potential of 70 eV.

Column chromatography was carried out on silica gel (Baker Chemical Co., 60-200 mesh). Thin layer chromatograms (TLC) were run on 8 x 4 cm (0.25 mm thick) strips of silica gel mixed with an UV indicator, Brinkmann Instruments, Inc., Sil G/UV_{254}, EM reagents No. 5539, or Eastman No. 13181. Developing solvents are listed for each sample and spots were detected by either UV light and/or exposure to iodine vapor. Flash chromatography carried out according to the method of Still *et al.*[17] using silica gel 40 μm particle size (J.T. Baker Chem. Co.).

The statement that "solvents were evaporated *in vacuo*" implies that the solvent was distilled using a rotary flash evaporator in a vacuum (20-30 Torr) at the minimum temperature possible using a water bath (30-90 ^{o}C). All pure samples were dried at room temperature over $CaCl_2$ or P_2O_5, *in vacuo*.

All solvents and reagents were used as purchased, unless otherwise specified. Dimethyl sulfoxide was dried by vacuum distillation from CaH_2 at a temperature not exceeding 90 ^{o}C. Petroleum ether refers to that fraction boiling at 30-60 ^{o}C. Brine refers to a saturated solution of NaCl. Trisodium phosphorothioate was prepared from thiophosphoryl chloride as described.[18]

a. Syntheses Leading up to and Using 1-(ω-Aminoalkyl)-2-aryladamantanes

1-Hydroxymethyl-2-phenyladamantane: To a cooled (10 ^{o}C) solution of 1-hydroxymethyl-2-bromoadamantane (1.8 g, 7.35 mmol) in dry benzene (150 mL) was added 2.53 g (9.51 mmol) of $AlBr_3$. The mixture was stirred at 10 ^{o}C for 2 h. (The reaction was followed by GC (SE-30 column, 150 to 250 ^{o}C at 10 ^{o}C/min) and was stopped as soon as the starting bromide disappeared. Unnecessarily long reaction times should be avoided as these may

result in lower yields. Retention times for the starting material and the product were 3.2 and 6.0 min, respectively. The mixture was then poured onto ice-water (200 mL) and extracted with chloroform (3 x 150 mL). The organic phase was washed with water, then with brine, dried ($MgSO_4$) and then solvents were evaporated, in vacuo. Flash chromatography of the residue (silica gel, 5-10% ethyl acetate in petroleum ether as an eluent) afforded the alcohol, initially an oil which slowly solidified to a waxy solid (1.7 g, 94%); mp 60-63 ^oC; IR (film), 3369, 3091, 3058, 3027, 2906, 2850, 1600, 1578, 1469, 1474, 1452, 1138, 1028, 757, 745, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.18-7.45 (m, Ph), 3.18 and 3.06 (AB, CH_2O, J = 11.1 Hz), 2.94 (br s, CHPh) 1.25-2.2 (m, 14H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 144.3 (C-i), 129.4 (C-o), 128.1 (C-m), 125.9 (C-p), 70.6 (CH_2OH), 52.9 (C-2), 42.4 (C-8), 40.0 (C-10), 38.2 (C-6), 37.7 (C-1), 35.1 (C-3), 34.1 (C-9), 31.2 (C-4), 28.8 (C-7), 27.8 (C-5); mass spectrum, m/e (relative intensity) 242 (16, M^+), 224 (36, M^+-H_2O), 211 (100, M^+-CH_2OH), 129 (30), 117 (20), 115 (14), 91 (94), 79 (35), 67 (18).

Anal. Calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.01; H, 9.26.

1-(Bromomethyl)-2-phenyladamantane: 1-(Hydroxymethyl)-2-phenyladamantane (2.42 g, 10 mmol) was refluxed with 48% HBr (15 mL) (9 h). The reaction was monitored periodically by GC (SE-30, isothermal, 200 ^oC; retention times of the starting alcohol and the product are 3.2 and 4.2 min, respectively). The mixture was cooled, diluted with water (100 mL), and extracted with $CHCl_3$ (3 x 100 mL). The organic layer was washed with water, sodium bicarbonate solution, and brine, and then dried ($MgSO_4$). The solvent was evaporated, in vacuo, to give 2.96 g (97%) of the bromide as a viscous liquid which solidified slowly to a waxy solid, mp 65-70 ^oC. GC/MS Analysis showed that the purity of the bromide is greater than 95%. The compound was used in the next step without further purification; ^1H NMR (360 MHz, $CDCl_3$) δ 7.42-

7.18 (m, 5H, Ph), 3.06 and 2.99 (AB, 2H, CH_2Br, J_{AB} = 10.0 Hz), 2.94 (br s, 1H, H-2), 2.34-1.62 (m, 13H, Adm); ^{13}C NMR (90 MHz, $CDCl_3$) δ 142.9 (Ph, C-i), 129.4 (Ph, C-o), 127.8 (Ph, C-m), 125.9 (Ph, C-p), 53.7 (C-2), 46.2 (CH_2Br), 43.4 (C-8), 39.5 (C-10), 37.5 (C-6), 36.2 (C-1), 36.0 (C-9), 35.0 (C-3), 30.4 C-1), 28.7 (C-7), 27.8 (C-5); mass spectrum, m/e (relative intensity) 306 and 304 (M^+, 28), 225 (M^+-Br, 56), 211 (19), 143 (11), 129 (12), 117 (14), 91 (100), 67 (10), 65 (10).

When the experiment was conducted on a larger scale (using 17.6 g of the alcohol, 0.072 mol), the reaction time had to be extended (16 h) to complete the reaction. Again, the reaction is best monitored by GC.

(2-Phenyl-1-adamantyl)acetonitrile: A mixture of the bromide, prepared above, (21.7 g, 70.9 mmol), NaCN (25 g), and dry DMSO (250 mL) was stirred at 80-100 ^{o}C for 15 h, after which it was poured into ice-water (700 mL) and extracted with hexane (4 x 200 mL). The hexane extract was washed twice with water, 6 N HCl (to remove any isocyanide), dried ($MgSO_4$) and evaporated, in vacuo, to give 16.9 g (95%) of an oil which crystallized slowly (2 weeks) to colorless needles; mp 67-68 ^{o}C; GC retention time = 4.6 min (SE-30 column, isothermal, 200 ^{o}C); IR (film) 2242 (CN) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.44-7.22 (m, 5H, Ph), 2.94 (b s, 1H, H-2), 1.95 (s, 2H, CH_2CN), 2.28-1.57 (m, 13H, remaining adamantane ring H's); ^{13}C NMR (90 MHz, $CDCl_3$) δ 142.7 (Ph, C-i), 129.4 (Ph, C-o), 128.3 (Ph, C-m), 126.5 (Ph, C-p), 117.6 (CN), 54.8 (C-2), 44.6 (C-8), 39.5 (C-10), 37.3 (C-6), 36.7 (C-9), 35.1 (C-1), 34.8 (C-3), 30.3 (C-4), 29.6 ($\underline{C}H_2CN$), 28.8 (C-7), 27.8 (C-5); mass spectrum, m/e (relative intensity) 251 (M^+, 51), 211 (M^+-CH_2CN, 64), 160 (13), 129 (20), 119 (27), 91 (100), 79 (28), 65 (13).

Anal. Calcd. for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57. Found: C, 86.15; H, 8.42; N, 5.39.

(2-Phenyl-1-adamantyl)acetamide: A mixture of the nitrile, prepared above (1.6 g, 6.37 mmol), methanol (15 mL), DMSO (0.5 mL), 30% H_2O_2 (1.1 mL), and 0.2 M NaOH (0.6 mL) was heated at 50-55 ^{o}C for 12 h (the reaction was monitored by GC; SE-30 column, isothermal, 200 ^{o}C, retention times of the starting nitrile and the amide are 4.6 and 8.8 min, respectively). The mixture was then diluted with water (100 mL) and extracted with $CHCl_3$ (3 x 75 mL). The organic layer was dried ($MgSO_4$) and evaporated, in vacuo. The residue was recrystallized from benzene-hexane and again from aqueous ethanol to give 1.35 g (79%) of the amide, mp 145-146 ^{o}C; IR (KBr) 3313 and 3185 (NH_2), 1655 (C=O), cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.45-7.21 (m, 5H, Ph), 5.33 and 4.92 (2 br s, 2H, NH_2), 2.99 (s, 1H, H-2), 2.37-1.50 (a series of complex multiplets, 15H, adm and $C\underline{H}_2CO$). The DOUBTFUL technique[19] was used to determine the chemical shift of the CH_2CO protons (dd, 2.05 and 1.85 ppm, J = 13.1 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.1 (C=O), 144.5 (Ph, C-i), 128.3 (Ph, C-o), 129.7 (Ph, C-o), 126.1 (Ph, C-p), 55.9 (C-2), 47.66 ($\underline{C}H_2C$=O), 44.9 (C-8), 39.8 (C-10), 38.4 (C-6), 37.8 (C-9), 35.9 (C-3), 35.7 (C-1), 29.2 (C-7), 28.3 (C-5); mass spectrum, m/e (relative intensity) 269 (M^+, 100), 252 (M^+-NH_3, 45), 224 (14), 211 (22), 210 (20), 178 (15), 136 (21), 119 (30), 115 (23), 91 (92), 79 (28), 77 (23), 67 (14), 65 (14).

Anal. Calcd. for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.19. Found: C, 80.56; H, 8.66; N, 5.02.

1-Amino-2-(2-phenyl-1-adamantyl)ethane Hydrochloride: Method A: A solution of (2-phenyl-1-adamantyl)acetamide (575 mg, 2.14 mmol) in anhydrous ether (250 mL) was refluxed with a suspension of lithium aluminum hydride (812 mg, 21.4 mmol) for 72 h. Excess lithium aluminum hydride was destroyed by the consecutive addition of water (0.8 mL), 10% NaOH solution (0.8 mL), and finally water (1.6 mL). The mixture was filtered and the precipitate was

washed with ether. The combined filtrate and washings were dried ($MgSO_4$) and solvents were removed, in vacuo. The residue was dissolved in anhydrous ether and treated with HCl gas in ether. The hydrochloride was filtered, and washed with ether. Recrystallization from ethanol-ether gave 544 mg (87%) of the product, mp 252-254 °C (decomp); IR (KBr) 3420, 2900-3100, 1600, 1495, 1475, 1455, 1395, 753, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.70 (br s, 3H, NH_3), 7.15-7.36 (m, 5H, Ph), 2.60-2.77 (m, 2H, CH_2), 2.70 (br s, 1H, H-2), 2.27-1.45 (m, 13H, Adm), 1.34-1.39 (m, 2H, C$\underline{H}_2$-Adm); ^{13}C NMR (90 MHz, $CDCl_3$) δ 143.9 (Ph, C-i), 129.3 (Ph, C-o), 128.4 (Ph, C-m), 126.2 (Ph, C-p), 55.2 (C-2), 44.8 (C-8), 39.8 (C-10), 38.4 ($\underline{C}H_2$-Adm), 38.0 (C-9), 37.8 (C-6), 35.8 (C-3), 35.1 (C-1), 34.9 ($\underline{C}H_2N$), 30.3 (C-4), 28.9 (C-7), 28.0 (C-5); mass spectrum, m/e (relative intensity) 255 (M^+-HCl, 9), 238 (M^+-HCl-NH_3), 226 (2), 177 (2), 155 (10), 135 (11), 129 (19), 128 (14), 115 (21), 106 (30), 93 (22), 91 (100), 79 (35), 77 (25), 67 (17).

Anal. Calcd. for $C_{18}H_{26}NCl$: C, 74.08; H, 8.98; N, 4.80. Found: C, 73.74; H, 8.85; N, 4.70.

Method B: To a solution of (2-phenyl-1-adamantyl)acetonitrile (11.9 g, 47.4 mmol) in methanol (500 mL) was added 12.3 g (94.8 mmol) of anhydrous $CoCl_2$. The mixture was stirred and cooled in ice while $NaBH_4$ (18.0 g, 0.474 mol) was added in small portions. Hydrogen evolved and a black precipitate of Co_2B was formed. Stirring was continued for 12 h after which the mixture was shaken with 6 N HCl (700 mL) to dissolve Co_2B. Neutral impurities were removed by extraction with hexane (200 mL). The acidic aqueous phase was then rendered strongly alkaline with concentrated NH_4OH (100 mL) and 10% NaOH solution (50 mL) and the amine was extracted by ether (4 x 300 mL). The ether layer was dried ($MgSO_4$) and evaporated, in vacuo. The residue was reacted with a methanolic solution of HCl. The hydrochloride (10.9 g, 83%)

crystallized out by slow dilution with anhydrous ether and was identical with the sample prepared by Method A.

N-[2-(2-Phenyl-1-adamantyl)ethyl]-2-chloroacetamidine Hydrochloride: Methyl chloroacetamidate was prepared, in situ, by stirring chloroacetonitrile (396 mg, 5.25 mmol) with a solution of sodium methoxide (prepared by dissolving sodium (20 mg, 0.0016 g atom) in 10 mL of anhydrous methanol) at room temperature for 1.5 h. A solution of the amine hydrochloride, prepared above, (1.46 g, 5.0 mmol) in anhydrous methanol (12.5 mL) was then added and the pH was adjusted to 4 by the addition of methanolic HCl. The mixture was stirred for 12 h after which the solvent was evaporated, in vacuo, at 60 ^{o}C and the residue was dissolved in 2-propanol (75 mL). NaCl was filtered and the filtrate was diluted slowly with anhydrous ether to afford the required chloroadmidine hydrochloride as colorless needles (1.01 g, 87%); mp 179-181 ^{o}C (decomp); ^{1}H NMR (360 MHz, $(CD_3)_2SO$) δ 9.94, 1.17 and 9.62 (s, 3H, NH), 7.51-7.18 (m, 5H, Ph), 4.33 (s, 2H, CH_2Cl), 3.23 and 3.12 (m, 2H, CH_2N), 2.88 (s, 1H, H-2), 1.46-2.26 (m, 13H, Adm), 1.30 (m, 2H, $C\underline{H}_2$-Adm); ^{13}C NMR (90 MHz, CD_3OD) δ 163.9 (NC=NH), 145.5 (Ph, C-i), 130.6 (Ph, C-o), 129.3 (Ph, C-m), 127.1 (Ph, C-p), 56.6 (C-2), 45.3 (C-10), 40.9 (C-8), 39.7 ($\underline{C}H_2Cl$), 39.4 ($\underline{C}H_2N$), 39.2 (C-9), 39.1 (Adm-$\underline{C}H_2$), 38.9 (C-6), 37.2 (C-3), 36.0 (C-1), 31.4 (C-4), 30.5 (C-7), 29.5 (C-5); mass spectrum, m/e (relative intensity) 330 (27), and 332 (9) (M^+-HCl), 295 (M^+-HCl-Cl, 8), 281 (M^+-HCl-CH_2Cl, 4), 238 (25), 129 (9), 128 (8), 121 (11), 119 (34), 108 (31), 106 (100), 105 (35), 91 (64), 79 (21).

Anal. Calcd. for $C_{20}H_{28}N_2Cl_2$: C, 65.39; H, 7.68; N, 7.63. Found: C, 64.84; H, 7.81; N, 7.57.

S-[N-[2-(2-Phenyl-1-adamantyl)ethyl]carbamidinium]methyl Hydrogen Phosphorothioate: A solution of the chloroamidine hydrochloride, prepared above (3.6 g, 9.81 mmol) in 50% aqueous ethanol (65 mL) was added to a

solution of trisodium phosphorothioate (1.857 g, 10.3 mmol) in water (15 mL). The mixture was stirred under nitrogen for 30 min after which it was rendered strongly acidic with methanolic HCl, concentrated, *in vacuo*, at room temperature to about half of its original volume and then diluted with 100 mL of water. The required phosphorothioate was filtered, washed thoroughly with water, ether, carbon disulfide, and finally with ether, and dried in a vacuum decsicator at room temperature. The yield was 3.65 g (91%); mp 158-162 ^{o}C (decomp); IR (KBr) 3400-2800 (NH_2, NH, POH), 1675, 1640 ($HNC{=}NH_2^+$) cm^{-1}; ^1H NMR (360 MHz, $(CD_3)_2SO$) δ 10.13, 10.08 (two b s, NH_2^+), 8.46 (br s, NH), 7.17-7.45 (m, 5H, Ph), 4.22 (br s, HOP/H_2O), 3.35 (d, 2H, CH_2SP, $^3J_{H,P}$ = 15.0 Hz), 3.11 and 3.00 (m, 2H, CH_2N), 2.86 (s, 1H, H-2), 1.45-2.25 (a series of complex multiplets, 13H, Adm), 1.28 (m, 2H, Adm-C$\underline{H}_2$); ^{13}C NMR (90 MHz, CD_3OD) δ 166.7 ($NHC{=}NH_2^+$), 145.5 (Ph, C-i), 130.7, 129.3 (Ph, C-o and C-m), 127.1 (Ph, C-p), 56.5 (C-2), 45.3 (C-8), 40.8 (C-10), 39.2 (2 overlapping signals), 39.1, 39.0 (C-9, C-6, CH_2CH_2NH) 37.2 (C-3), 36.0 (C-1), 31.4 (C-4), 30.4 (CH_2S), 30.5 (C-7), 29.5 (C-5); mass spectrum, *m/e* (relative intensity) 296 (M^+-SPO_3H, 10), 255 (15), 238 (8), 192 (14), 117 (30), 91 (100), 72 (71), 65 (35).

Anal. Calcd. for $C_{20}H_{29}N_2SPO_3 \cdot 1/4H_2O$: C, 58.16; H, 7.20; N, 6.78; S, 7.76. Found: C, 58.07; H, 7.51; N, 6.40; S, 7.61.

N-[2-(2-Phenyl-1-adamantyl)ethyl]-2-mercaptoacetamidine Hydrochloride: A solution of the phosphorothioate, prepared above (3.65 g, 8.94 mmol) in ethanol (50 mL) containing 6 N HCl (100 mL), was refluxed for 20 min under a blanket of N_2. The mixture was then cooled to room temperature, concentrated, *in vacuo*, to one-half of its original volume and diluted with cold water (100 mL). The mercaptan separated as a gummy solid which was filtered, washed with water and finally with ether, dried under high vacuum (1 Torr) at room temperature to give shiny flakes (3.03 g, 92 %); mp 83-95 ^{o}C (decomp); IR

(KBr) 3200 (br, NH), 2478 (SH), 1677, 1636 ($NHC{=}NH_2^+$) cm^{-1}; ^1H NMR (360 MHz, CD_3OD) δ 7.48-7.18 (m, 5H, Ph), 3.35 (s, 2H, CH_2S), 3.23-3.14 (M, 2H, CH_2N), 2.93 (br s, 1H, H-2), 2.34 (m, 1H, H-4), 2.15-1.46 (m, 12H, remaining Adm H's), 1.36 (m, 2H. $C\underline{H}_2$-Adm); ^{13}C NMR (90 MHz, CD_3OD) δ 168.2 ($NHC{=}NH_2^+$), 145.5 (Ph, C-i), 130.7, 129.3 (Ph, C-o and C-m), 127.1 (Ph, C-p), 56.5 (C-2), 45.3 (C-8), 40.9 (C-10), 39.2 (two overlapping signals: $\underline{C}H_2$-Adm, C-9), 39.09 (CH_2N), 39.00 (C-6), 37.2 (C-3), 36.0 (C-1), 31.5 (C-4), 30.5 (C-7), 29.5 (C-5), 25.0 (CH_2SH); mass spectrum, m/e (relative intensity) 297 (10), 296 (51), 295 (23), 255 (15), 238 (31), 131 (31), 115 (28), 91 (77), 85 (43), 72 (92), 69 (100), 58 (28).

Anal. Calcd. for $C_{20}H_{29}N_2ClS$: C, 65.82; H, 8,01; N, 7.68; S, 8.78. Found: C, 66.29; H, 7.91; N, 7.14; S, 8.02.

b. Syntheses Leading up to and Using 1-Aryl-2-(ω-aminoalkyl)-adamantanes

N-[(1-Phenyl-2-adamantyl)methyl]-2-chloroacetamidine Hydrochloride: Chloroacetonitrile (1.63 g, 21.6 mmol) was added to a solution of sodium methoxide [prepared from sodium (0.019 g, 2.16 g atom) and anhydrous methanol (30 mL)] and the mixture was stirred at room temperature for 1.5 h. A solution of N-(1-phenyl-2-adamantyl)methylamine hydrochloride (5.72 g, 20.6 mmol) in methanol (50 mL) was added and the pH of the solution was adjusted to about 4 (or lower) by adding methanolic HCl. The mixture was stirred at ambient temperature overnight (16 h). A small quantity of a white precipitate was filtered off. The filtrate was evaporated. in vacuo, and the residue was washed thoroughly with water (100 mL) and ether (100 mL) to afford a white powder (5.71 g, 78%), mp 268-271 °C (decomp). A small amount of the solid was recrystallized from methanol/ether to furnish colorless needles, mp 270-272 °C (decomp); IR (KBr) 1687 ($C{=}NH_2^+$), 1644 cm^{-1} (C=N); ^1H NMR

($DMSO-\underline{d}_6$) δ 9.93, 9.46, 9.09 (three br s, 3 NH's), 7.30 (s, 5H, ArH), 4.32 (s, 2H, $C\underline{H}_2Cl$), 2.84-1.04 (m, 16H, AdH).

Anal. Calcd. for $C_{19}H_{26}N_2Cl_2$ (353.34); C, 64.59; H, 7.42; N, 7.93. Found: C, 64.37; H, 7.28; N, 7.90.

N-[2-(1-Phenyl-2-adamantyl)ethyl]-2-mercaptoacetamidinium Hydrochloride: An aqueous solution of trisodium phosphorothioate (2.43 g, 13.5 mmol in 38 mL) was added to a suspension of N-[2-(1-phenyl-2-adamantyl)-ethyl]-2-chloroacetamidine hydrochloride[4,5] (4.72 g, 12.8 mmol) in 50% ethanol (72 mL). The mixture was allowed to stir at ambient temperature for 30 min under a stream of nitrogen. To the homogeneous solution was added 6 N HCl (61.5 mL) and the mixture was heated at 85-90 °C for 20 min. Upon cooling, a white solid (3.98 g, 85%) precipitated which was filtered and washed thoroughly with water, mp 182-186 °C (decomp). Recrystallization from ethanol-ether gave a white powder (2.80 g), mp 191-193 °C (decomp); IR (KBr) 1679 ($C{=}NH_2^+$), 1643 cm^{-1} (C=N); ^1H NMR ($DMSO-\underline{d}_6$) δ 9.75, 9.38, 8.61 (three br s, 3H, exchangeable with D_2O, 3 NH's), 7.30 (s, 5H, Ph), 3.89 (br s, 1H, exchangeable with D_2O, SH), 3.31 (br s, 2H, $C\underline{H}_2S$), 2.96 (br s, 2H, $C\underline{H}_2N$), 2.26-0.50 (m, 16H, Adh).

Anal. Calcd. for $C_{20}H_{29}N_2ClS$ (364.97): C, 65.82; H, 8.01; N, 7.68; S, 8.78. Found: C, 66.03; H, 8.12; N, 7.48; S, 8.68.

S-[N-(1-Phenyl-2-adamantyl)methyl]carboxamidinium]methyl Hydrogen Phosphorothioate: Into a 200 mL 2-necked flask equipped with a magnetic stirrer and rubber septa was charged trisodium phosphorothioate (2.00 g, 11.1 mmol). After flushing with N_2, the solid was dissolved in water (15 mL) by stirring. N-(1-Phenyl-2-adamantyl)methyl-2-chloroacetamidine hydrochloride[4,5] (3.74 g, 10.6 mmol) in 50% ethanol (70 mL) was added and the mixture was stirred at room temperature (30 min). Insoluble solids were filtered off and

to the filtrate was added 6 N HCl (30 mL) dropwise, with vigorous stirring. The acidic mixture was stirred at room temperature for 20 min longer and then at 0 ^{o}C and then stood for 1 h. The colorless precipitate was filtered (the filtrate was acidic) and washed successively with water (20 mL), ethanol (20 mL), toluene (20 mL) and dried, in vacuo. It weighed 3.64 g (87%), mp 217-219 ^{o}C (decomp); IR (KBr) 1678 ($C{=}NH_2^+$), 1642 cm^{-1} (C=N); ^{1}H NMR (DMSO and TFA) δ 9.23, 9.07, 8.61 (three br s, NH's), 7.33 (s, 5H, ArH), 3.58 (d, 2H, CH_2-S-P, J = 16.2 Hz), 2.74-1.09 (m, 16H, AdH).

Anal. Calcd. for $C_{19}H_{27}N_2SPO_3$ (394.47): C, 57.85; H, 6.90; N, 7.10; S, 8.12. Found: C, 58.12; H, 7.21; N, 6.97; S, 8.31.

1-(4-Fluorophenyl)-2-adamantanol: A solution of 4-protoadamantanone (6.06 g, 4.03 mmol) in THF (50 mL) was added to the Grignard reagent prepared from magnesium turnings (1.03 g, 42.3 mmol) and 1-bromo-4-fluorobenzene (7.78 g, 44.5 mmol) in THF (50 mL). The mixture was refluxed (4 h) and was quenched with NH_4Cl, and extracted with ether (3 x 100 mL). The combined ether layers were washed with saturated sodium bicarbonate solution (100 mL) then water (2 x 100 mL) and were dried ($MgSO_4$). The solvent was removed, in vacuo, and the residue was refluxed with 98% formic acid (200 mL) for 30 min. Solvents were removed, in vacuo, and the residue was dissolved in acetone (200 mL) and was boiled with 1 N HCl (80 mL) (2 h). Volatile materials were distilled, in vacuo, and the residue was extracted with ether (3 x 100 mL). The extracts were washed with sodium bicarbonate solution (3 x 100 mL), water (2 x 100 mL) and were dried ($MgSO_4$). Solvents were removed, in vacuo, yielding a light brown thick oil. Upon triturating with petroleum ether, a beige powder (6.64 g, 67%) was obtained, mp 87-90 ^{o}C. After recrystallization from hexane, the beige product (6.16 g) was obtained, mp 88-90 ^{o}C. A small amount of the same was recrystallized repeatedly from hexane, to produce colorless prisms,

mp 89.5-91.5 °C; IR (KBr) 3424 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 7.81-6.77 (m, 4H, Ar), 3.97 (br s, 1H, CH-O) 3.01-0.83 (m, 14H, AdH).

Anal. Calcd. for $C_{16}H_{19}FO$ (246.33): C, 78.02; H, 7.77. Found: C, 78.12; H, 7.84.

1-(4-Fluorophenyl)-2-adamantanone: A Jones-Djerassi reagent was prepared according to the literature[20] by diluting a solution of 26.72 g of chromium trioxide in 23 mL of conc. sulfuric acid with water to reach a volume of 100 mL.

This Jones-Djerassi reagent (18.5 mL) was added dropwise to a prechilled (-10 °C) solution of 1-(4-fluorophenyl)-2-adamantanol (10 g, 40.6 mmol) in acetone (185 mL) and water (30 mL). The mixture was allowed to stir at 15 °C for 3.5 h. Excess oxidant was destroyed by adding methanol (30 mL). Low boiling point materials were removed, in vacuo, and the residue diluted with water (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water (5 x 200 mL), saturated sodium bicarbonate solution (2 x 200 mL), water (2 x 200 mL), and were dried ($MgSO_4$). Colorless prisms (9.27 g, 94%) mp 160-163.5 °C were obtained after solvents were removed, in vacuo. A small amount of the product was recrystallized from ether/hexane to furnish colorless plates, mp 162.5-164.5 °C; IR (KBr) 1712 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 7.28-6.68 (m, 4H, Ar), 2.60 (br s, 1H, CHC=O), 2.70-1.85 (m, 12H, AdH).

Anal. Calcd. for $C_{16}H_{17}FO$ (244.32): C, 78.66; H, 7.02. Found: C, 78.41; H, 7.07.

1-(4-Fluorophenyl)-2-(cyanomethylene)adamantane: A solution of diethyl cyanomethylphosphonate (8.71 g, 49.1 mmol) in THF (20 mL) was added to a stirred suspension of sodium hydride (50% in paraffin, 2.36 g, 49.1 mmol) in ice-cold THF (3 mL). The mixture was stirred at room temperature for 10 min,

followed by the addition of 1-(4-fluorophenyl)-2-adamantanone (9.24 g, 37.8 mmol) in THF (60 mL). The mixture was stirred at ambient temperature (20 h) and, then at 55 ^{o}C (4 h). The clear supernatant was decanted from a brown gummy residue, which was washed thoroughly with THF. The combined THF layers were evaporated, in vacuo, and the residue was chromatographed on a short column of alumina (F-20) in hexane. A colorless solid (9.76 g, 97%) was obtained, after evaporating the eluate, in vacuo. A small amount of this solid was recrystallized repeatedly from hexane, to form colorless crystals, mp 84-85 ^{o}C; IR (KBr) 2214 (C≡N), 1614 cm^{-1} (C=C); ^{1}H NMR (CCl_4) δ 7.40-6.80 (m, 4H, Ar), 4.26 (s, 1H, CH-CN), 3.35 (br s, 1H, CH-C=), 2.55-1.80 (m, 12H, AdH).

Anal. Calcd. for $C_{18}H_{18}FN$ (267.35): C, 80.87; H, 6.78; N, 5.24. Found: C, 80.52; H, 6.67; N, 5.17.

1-(4-Fluorophenyl)-2-(cyanomethyl)adamantane: 1-(4-Fluorophenyl)-2-(cyanomethylene)adamantane (6.0 g, 22.4 mmol) in absolute ethanol (120 mL) was hydrogenated (Parr apparatus) in the presence of 10% Pd/C (1.2 g) as the catalyst under 50 psi hydrogen pressure for 24 h at ambient temperature. The catalyst was filtered and washed thoroughly with ethanol, and the filtrate was evaporated, in vacuo, to furnish a colorless solid (5.91 g, 98%), mp 66.5-70.5. Repeated recrystallization from hexane gave colorless fine needles, mp 75-77 ^{o}C; IR (KBr) 2245 cm^{-1} (C≡N); ^{1}H NMR (CCl_4) δ 7.40-6.70 (m, 4H, Ar), 2.40-1.12 (m, 16H, AdH).

Anal. Calcd. for $C_{18}H_{20}FN$ (269.37): C, 80.26; H, 7.48; N, 5.20. Found: C, 80.19; H, 7.55; N, 5.12.

[1-(4-Fluorophenyl)-2-adamantyl]acetamide: A solution of 30% H_2O_2 (10.1 mL) was added to a stirred ice-cold mixture of 1-(4-fluorophenyl)-2-(cyanomethyl)adamantane (5.39 g, 20 mmol), DMF (15 mL), ethanol (200 mL) and 6 N NaOH (10.1 mL). The mixture was then stirred at 50 ^{o}C for 7 h, until

the starting material had disappeared (TLC). Most volatile materials were removed, in vacuo, and the residue was dissolved in ether (120 mL). The ether solution was washed with H_2O (50 mL), was dried ($MgSO_4$), and was evaporated. in vacuo. A white powder (4.54 g, 83%) was obtained, mp 138-141 ^{o}C. A small amount of the sample was recrystallized repeatedly from ether/pet. ether, after which colorless fine prisms, mp 140.5-142.5 ^{o}C, was obtained; IR (KBr) 1657 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.50-6.70 (m, 4H, Ar), 5.15 (br s, 2H, $CONH_2$), 2.46 (br s, 2H, CH_2CO), 2.35-0.99 (m, 14H, AdH).

Anal. Calcd. for $C_{18}H_{22}FNO$ (287.39): C, 75.23; H, 7.72; N, 4.87. Found: C, 75.00; H, 7.54; N, 4.78.

1-Amino-2-[1-(4-Fluorophenyl)-2-adamantyl]ethane Hydrochloride: A solution of [1-(4-fluorophenyl)-2-adamantyl]acetamide (4.2 g, 14.6 mmol) in THF (40 mL) was added dropwise to a suspension of $LiAlH_4$ (2.77 g, 73.0 mmol) in THF (110 mL) at 0-5 ^{o}C. The mixture was allowed to reflux (24 h), cooled and treated successively with water (2.77 mL), 15% NaOH (2.77 mL), and water (8.31 mL). The mixture was refluxed for 10 min, cooled and the white ppte was filtered and washed thoroughly with ether. The combined filtrate and washings were evaporated, in vacuo, and the residue was dissolved in dry ether (30 mL) and dried ($MgSO_4$) again. The ether solution was filtered, HCl gas was bubbled through the filtrate. The colorless salt (3.56 g, 79%) was filtered off, mp 239-243 ^{o}C. A small quantity of this solid was recrystallized repeatedly from ethanol/hexane to raise the mp to 242.5-244 ^{o}C; IR (KBr) ~3125 cm^{-1} (NH_3^{+}); ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 7.82 (br s, 3H, exchangeable with D_2O, NH_3^{+}), 7.22 (m, 4H, Ar), 2.50 (m, 2H, CH_2N), 3.20-0.82 (m, 16H, AdH).

Anal. Calcd. for $C_{18}H_{25}ClFN$ (309.86): C, 69.77; H, 8.13; N, 4.52. Found: C, 69.98; H, 8.18; N, 4.45.

N-{2-[1-(4-Fluorophenyl)-2-adamantyl]ethyl}-2-chloroacetamidine Hydrochloride: Chloroacetonitrile (0.83 g, 11 mmol) was added to a solution of sodium methoxide [prepared from sodium (0.025 g, 1.1 mg/atom) and dry methanol (11 mL)] and the mixture was allowed to stir at ambient temperature for 1.5 h. A solution of 2-[1-(4-fluorophenyl)-2-adamantyl]ethylamine hydrochloride (3.10 g, 10 mmol) in methanol (22 mL) was added and the pH of the solution was adjusted to about 4 by adding methanolic HCl. The mixture was allowed to stir at room temperature for 6 h. Solvents were removed, in vacuo, and the semi-solid was triturated with pet. ether. A colorless solid (4.0 g) was obtained, which was washed thoroughly with water and dried in a desiccator in the presence of P_2O_5. The dry solid (2.82 g, 73%) melted at 191-197 $^{\circ}C$ (decomp). After repeated recrystallization from ethanol/pet. ether, the colorless prisms melted at 203.5-204.5 $^{\circ}C$ (decomp.); IR (KBr) 1686 cm^{-1} ($C{=}NH_2^+$), 1649 cm^{-1} (C=N); ^1H NMR (DMSO-d_6) δ 10.16, 9.60. 9.09 (three br s, 3H, $NHC(=NH_2^+)$), 7.40-6.90 (m, 4H, Ar), 4.43 (s, 2H, CH_2Cl), 3.05 (br s, 2H, CH_2N), 2.50-0.68 (m, 16H, AdH).

Anal. Calcd. for $C_{20}H_{27}Cl_2N_2F$ (385.36): C, 62.34; H, 7.06; N, 7.27. Found: C, 61.75; H, 7.00; N, 7.30.

S-{N-{2-[1-(4-Fluorophenyl)-2-adamantyl]ethyl}carboxamidinium}methyl Hydrogen Phosphorothioate Monohydrate. A solution of N-{2-[1-(4-fluorophenyl)-2-adamantyl]ethyl}-2-chloroacetamidine hydrochloride (5.50 g, 14.28 mmol) in ethanol (40 mL) was added to an aqueous solution of trisodium phosphorothioate (2.7 g, 15 mmol in 24 mL) under a blanket of nitrogen. The mixture was allowed to stir at ambient temperature for 30 min. The solution was filtered and the filtrate was acidified with 1 N HCl (32 mL), with ice-cooling. Volatile solvents were distilled, in vacuo, and the aqueous supernatant was decanted from a gummy residue, which was triturated with ether, to

eventually yield a solid (5.46 g) which was washed successively with ether, toluene, carbon disulfide, ether, and the recrystallized from ethanol/ether. A white powder (3.14 g, 52%) was obtained, mp 175-178 ^{o}C (decomp); IR (KBr) 1677 ($C{=}NH_2^+$), 1640 cm^{-1} (C=N); ^{1}H NMR (DMSO-$\underline{d}_6$) δ 10.27, 8.27 (two br s, exchangeable with NH and OH protons), 7.25 (m, 4H, Ar), 3.38 (d, 2H, J = 15 Hz, $C\underline{H}_2S$), 2.94 (br s, 2H, $C\underline{H}_2N$), 2.50-1.10 (m, 16H, AdH).

Anal. Calcd. for $C_{20}H_{30}FN_2O_4PS$ (444.50): C, 54.04; H, 6.80; N, 6.30; S, 7.21. Found: C, 53.80; H, 6.42; N, 6.24; S, 7.30.

1-(4-Methoxyphenyl)-2-adamantanol: A solution of 4-methoxyphenylmagnesium bromide was prepared by refluxing a mixture of 4-bromoanisole (3.6 g, 0.019 mol) and magnesium turnings (0.38 g, 0.016 mol) in THF (30 mL), until most of the magnesium had disappeared. This Grignard solution was added dropwise to a solution of 4-protoadamantanone (2.0 g, 0.013 mol) in THF (20 mL) and the mixture was refluxed (3 h). The reaction mixture was worked up in the customary manner: quenched with NH_4Cl (10 mL), extracted with ether (3 x 20 mL), washed with water (20 mL), saturated bicarbonate solution (20 mL), and again with water (20 mL) and then dried ($MgSO_4$). Solvents were removed, in vacuo, and the residue was refluxed with 98% formic acid (100 mL) for 30 min. The mixture was evaporated in vacuo, and the residue was dissolved in acetone (100 mL) and was hydrolyzed by refluxing with 1 N HCl (40 mL) for 2 h. Volatile materials were removed, in vacuo, and the residue was extracted with ether (3 x 50 mL). The combined ether layers were washed with water (50 mL), saturated sodium bicarbonate solution (2 x 50 mL), water (50 mL) and then dried ($MgSO_4$). Solvents were distilled, in vacuo, and the yellow residual solid was recrystallized from hexane to produce ivory prisms (2.50 g, 74%), mp 94-97.5 ^{o}C. One more recrystallization from ether/hexane gave white fine plates, mp 99.5-101.5 ^{o}C; IR (KBr) 3565, 3544, 3437 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$) δ 7.31

and 6.88 M, AA'XX' aromatic system), 3.94 (br s, 1H, CHO), 3.79 (s, 3H, OCH_3), 2.91-1.16 (m, 13H, AdH), 1.44 (s, 1H, OH, exchangeable with D_2O).

Anal. Calcd. for $C_{17}H_{22}O_2$ (258.35): C, 79.03; H, 8.58. Found: C, 78.10; H, 8.50.

1-(4-Methoxyphenyl)-2-adamantanone: A solution of 1-(4-methoxyphenyl)-2-adamantanol (1.5 g, 5.8 mmol) in acetone (18 mL) was added to a mixture of potassium dichromate (1.20 g, 4.08 mmol), conc. H_2SO_4 (1.01 mL, Sp. Gr. 1.84), water (6.13 mL) and acetone (9 mL), with cooling (-10 - 0 °C). The mixture was allowed to stir at this temperature (-10 - 0 °C) for 2 h. Excess dichromate was destroyed by the addition of methanol (5 mL). The granular ppte was filtered and washed thoroughly with ethyl acetate. The water layer was extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate layers were washed with water (20 mL), saturated sodium bicarbonate solution (3 x 20 mL), water (2 x 20 mL) and then dried ($MgSO_4$). Solvents were removed, in vacuo, to furnish a light yellow solid (1.33 g), mp 88-92 °C. This solid was recrystallized from hexane to produce colorless prisms (1.30 g, 87%), mp 88-92 °C. A small amount of the solid upon repeated recrystallization from hexane afforded colorless prisms, mp 96-99 °C; IR (KBr) 1718 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.17, 6.87 (two m of AA'XX' aromatic system, 4H), 3.79 (s, 3H, OCH_3), 3.22-1.50 (m, 13H, AdH).

Anal. Calcd. for $C_{17}H_{20}O_2$ (256.33): C, 79.65; H, 7.86. Found: C, 79.61; H, 7.87.

1-(4-Methoxyphenyl)-2-(cyanomethylene)adamantane: A solution of diethyl cyanomethylphosphonate (3.64 g, 20.6 mmol) in THF (20 mL) was added to a suspension of sodium hydride (50% in paraffin, 0.99 g, 20.6 mmol) in THF (20 mL), with ice-cooling. The mixture was allowed to stir at ambient temperature for 10 min followed by the addition of 1-(4-methoxyphenyl)-2-

adamantanone (4.8 g, 18.7 mmol) in THF (30 mL). After standing at room temperature for 24 h, the clear supernatant was decanted from a brown gummy ppte and the residue washed thoroughly with THF. The combined THF solutions were passed through a short column of alumina (30 g, Alumina F-20, THF) using as the eluting solvent. The colorless solid which was obtained was recrystallized from THF hexane to give colorless prisms (4.47 g, 86%), mp 153-157 ^{o}C. A small amount of the sample was repeatedly recrystallization ether/hexane to produce colorless prisms, mp 160.5-162.5 ^{o}C; IR (KBr) 2210 (C≡N), 1611 cm^{-1} (C=C); ^{1}H NMR (CCl_4) δ 7.17, 6.78 (m s, 4 aromatic H's), 4.30 (s, 1H, =CH-), 3.77 (s, 3H, OCH_3), 3.34 (br s, 1H, CH-C=), 2.50-1.80 (m, 12H, AdH).

Anal. Calcd. for $C_{19}H_{21}NO$ (256.33): C, 81.68; H, 7.58; N, 5.01. Found: C, 81.86; H, 7.74; N, 4.97.

1-(4-Methoxyphenyl)-2-(cyanomethyl)adamantane: 1-(4-Methoxyphenyl)-2-(cyanomethylene)adamantane (0.56 g, 2mmol) was hydrogenated with a Parr apparatus in freshly-distilled ethyl acetate (20 mL) over 10% Pd/C (0.1 g) as catalyst, under 40 psi hydrogen pressure for 20 h at ambient temperature. The catalyst was filtered off, and washed with ethanol. The filtrate was evaporated, in vacuo. and furnished colorless prisms (0.50 g, 89%), mp 127-128 ^{o}C. Repeated recrystallization from ether/AcOEt/hexane gave colorless prisms, mp 129-130.5 ^{o}C; IR (KBr) 2239 cm^{-1} (C≡N); ^{1}H NMR ($CDCl_3$) δ 7.18, 6.86 (two m's, 4H, Ar), 3.79 9s, 3H, OCH_3), 3.15-1.40 (m, 16H, AdH).

Anal. Calcd. for $C_{19}H_{23}NO$ (281.38): C, 81.10; H, 8.24; N, 4.98. Found: C, 81.33; H, 8.35; N, 4.88.

[1-(4-Methoxyphenyl)-2-adamantyl]acetamide: A solution of 30% H_2O_2 (0.72 mL) was added to a mixture of 1-(4-methoxyphenyl)-2-(cyanomethyl)adamantane (0.4 g, 1.42 mmol) in DMSO (3 mL), ethanol (14 mL), THF (24 mL) and 6 N NaOH (0.72 mL) (ice-cooling). The mixture was stirred at 50 ^{o}C (3 h) until

the starting material had disappeared (TLC). Volatile solvents were removed, in vacuo. Water (5 mL) was added to the residue, and the white ppte was filtered and washed thoroughly with water. After recrystallization from THF/hexane, a colorless fluffy solid (0.39 g, 92%) was obtained, mp 151.5-153.5 ^{o}C. Further recrystallization with THF/hexane did not raise the mp; IR (KBr) 1661 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 7.25, 6.84 (m's, 4 Ar H's), 5.29 (br s, 2H, $CONH_2$), 3.78 (s, 3H, OCH_3), 2.80-1.54 (m, 16H, AdH).

Anal. Calcd. for $C_{19}H_{25}NO_2$ (299.40): C, 76.22; H, 8.42; N, 4.68. Found: C, 76.21; H, 8.57; N, 4.55.

1-Amino-2-[1-(4-methoxyphenyl)-2-adamantyl]ethane Hydrochloride: A solution of [1-(4-methoxyphenyl)-2-adamantyl]acetamide (4.15 g, 13.9 mmol) in THF (40 mL) was added dropwise to an ice-cold suspension of LAH (2.63 g, 69.3 mmol) in THF (100 mL). The mixture was refluxed for 20 h. After cooling, the reaction mixture was quenched by the successive addition of water (2.63 mL), 15% NaOH (2.63 mL), and water (7.89 mL). The mixture was refluxed (10 min) cooled, filtered and the white ppte was washed thoroughly with ether. The organic extracts were dried ($MgSO_4$) and evaporated, in vacuo. The residue was dissolved in anhydrous ether, filtered to remove some insoluble materials, and HCl gas bubbled through the filtrate. Colorless fine prisms (3.62 g, 85%) were obtained, mp 255-257 ^{o}C. Repeated recrystallization from ethanol/ether furnished colorless fine needles, mp 255-257 ^{o}C; IR (KBr) ~3125 cm^{-1} (NH_3^+); ^{1}H NMR (DMSO-d_6) δ 7.79 (br s, 3H, exchangeable with D_2O, NH_3^+), 7.23, 6.86 (m's, 4 Ar H's), 3.73 (s, 3H, OCH_3), 2.49 (br s, 2H, CH_2-N), 2.84-0.65 (m, 16H, AdH).

Anal. Calcd. for $C_{19}H_{28}ClNO$ (321.89): C, 70.90; H, 8.77; N, 4.35. Found: C, 71.16; H, 8.92; N, 4.56.

N-{2-[1-(4-Methoxyphenyl)-2-adamantyl]ethyl}-2-chloroacetamidinium Hydrochloride: Chloroacetonitrile (0.66 g, 8.69 mmol) was added to a solution of sodium methoxide [prepared from sodium (0.02 g, 0.89 mmol) and anhydrous methanol (10 mL)] and the mixture was stirred at ambient temperature for 1.5 h. A solution of 2-[1-(4-methoxyphenyl)-2-adamantyl]ethylamine hydrochloride (2.53 g, 7.86 mmol) in MeOH (24 mL) was added and the pH of the solution was adjusted to about 4 by adding methanolic hydrogen chloride. The mixture was stirred at room temperature for 5 h. The solution was evaporated, in vacuo, and the residue was triturated with ether. A colorless solid (3.02 g, 97%) was isolated, mp 200-202 °C (decomp). Small amounts of this sample was recrystallized repeatedly from ethanol/ether to afford colorless fine prisms, mp 206.5-208.5 °C (decomp); IR (KBr) 1688 ($C{=}NH_2^+$), 1649 cm^{-1} (C=N); ^1H NMR ($DMSO\text{-}d_6$) δ 10.05, 9.53, 9.04 (three br s, 3H, 3NH's), 7.22, 6.85 (2 m's, 4 Ar H's), 4.37 (s, 2H, CH_2Cl), 3.73 (s, 3H, OCH_3), 3.09 (br s, 2H, CH_2NH), 2.35-0.66 (m, 16H, AdH).

Anal. Calcd. for $C_{21}H_{30}Cl_2N_2O$ (397.39): C, 63.47; H, 7.61; N, 7.05. Found: C, 63.47; H, 7.77; N, 7.16.

Dihydrogen S-{N-{2-[1-(4-Methoxyphenyl)-2-adamantyl]ethyl}-carboxamidinium}methyl Phosphorothioate Monohydrate: A solution of trisodium phosphorothioate (2.04 g, 11.31 mmol) in water (18 mL) was added, dropwise, to a solution of N-{2-[1-(4-methoxyphenyl)-2-adamantyl]ethyl}-2-chloroacetamidinium hydrochloride (4.28 g, 10.8 mmol) in ethanol (7 mL) at room temperature, under N_2. The mixture was stirred for 30 min at 25 °C, was filtered, and the filtrate was acidified with 1 N HCl (25 mL). Volatile solvents were removed, in vacuo, and the clear supernatant was decanted and the residue was first washed with water and then triturated with ether. A light grey solid (4.46 g) was obtained, which was washed successively with ether,

toluene, carbon disulfide, ether and then recrystallized from ethanol/ether to form a colorless solid (2.37 g, 48%), mp 170-172 ^{o}C (decomp); IR (KBr) 1678 ($C{=}NH_2^+$), 1643 cm^{-1} (C=N); ^{1}H NMR (DMSO-$\underline{d}_6$/$CDCl_3$) δ 10.18, 8.23 (two br s, 4H, 2NH, 2OH), 7.23, 6.85 (2 m's, 4 Ar H), 3.73 (s, 3H, OCH_3), 3.37 (d, 2H, J = 15 Hz, CH_2-S), 2.91 (br s, 2H, CH_2-N), 2.50-0.50 (m, 16H, AdH).

Anal. Calcd. for $C_{21}H_{33}N_2O_5PS$ (456.53): C, 55.25; H, 7.29; N, 6.14; S, 7.02. Found: C, 55.15; H, 7.06; N, 6.11; S, 6.76.

1-(4-Methylthiophenyl)-2-adamantanol: 4-Methylthiophenylmagnesium bromide was prepared by refluxing a mixture of p-bromothioanisole (14.9 g, 73.26 mmol), magnesium turnings (1.70 g, 69.9 mmol) and dry THF (70 mL) for 45 min until most of the magnesium turnings had disappeared. A solution of 4-protoadamantanone (10 g, 66.6 mmol) in THF (30 mL) was added dropwise and the mixture was refluxed for 3.5 h, cooled and treated with saturated ammonium chloride solution (15 mL). The white ppte which was formed was filtered and washed thoroughly with ether. The combined organic layers were washed with water (2 x 50 mL) and dried ($MgSO_4$). The solution was evaporated, in vacuo, and the residue was allowed to reflux with 98% formic acid (200 mL) for 0.5 h. Solvents were removed, in vacuo, and the residue was dissolved in acetone (200 mL) and hydrolyzed by boiling with 1 N HCl (100 mL) for 2 h. The reaction mixture was evaporated, in vacuo, and the residue was extracted with ether (3 x 100 mL). The combined ether layers were washed with water (2 x 150 mL), aqueous sodium bicarbonate solution (2 x 150 mL), water (150 mL) and were dried ($MgSO_4$). After removing solvents, in vacuo, a soft light yellow solid (16.05 g) was obtained which was triturated with hexane to give a light yellow powder (12.11 g, 67%), mp 104-115 ^{o}C. Repeated recrystallization from ether/hexane furnished colorless fine plates, mp 122.5-124 ^{o}C; MS, $\underline{m/e}$ 274 (M^+); IR (KBr) 3573, 3557, 3458 cm^{-1} (OH); ^{1}H NMR

(CCl_4) δ 7.19 (s, 4H, Ar), 3.84 (br s, 1H, C<u>H</u>O), 2.43 (s, 3H, SCH_3), 2.70-1.15 (m, 12H, AdH), 1.05 (s, 1H, OH, exchangeable with D_2O).

Anal. Calcd. for $C_{17}H_{22}OS$ (274.43): C, 74.41; H, 8.08. Found: C, 74.27; H, 8.12.

1-(4-Methylthiophenyl)-2-adamantanone: This oxidation procedure is a modification of a known method.[11] A solution of trifluoroacetic anhydride (0.79 g, 3.75 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise to a solution of DMSO (0.36 mL, 5 mmol) in CH_2Cl_2 (3 mL) at -65 °C (under nitrogen) and the mixture was allowed to stir at -65 °C for 10 min. A solution of 1-(4-methylthiophenyl)-2-adamantanol (0.69 g, 2.5 mmol) in CH_2Cl_2 (2 mL) was then added and the mixture was allowed to stir at -65 °C (or lower) for 5 min. Triethylamine (1 mL) was added at -78 °C. The cooling bath was removed and the mixture was permitted to come to ambient temperature and stirred at that temperature for 30 min. After stirring at room temperature for another 10 min, the mixture was washed with water (2 x 10 mL), the organic layer was separated and was dried ($MgSO_4$). Removal of solvents, <u>in vacuo</u>, produced a light yellow solid (0.79 g) which was purified by column chromatography (Alumina F-20, ethyl acetate/chloroform, 1/20). A colorless solid (0.65 g, 96%) was obtained, mp 82-85 °C. Repeated recrystallization from CH_2Cl_2/hexane gave white plates with mp 87-89 °C; IR (KBr) 1717 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 7.19 (s, 4H, Ar), 2.46 (s, 3H, SCH_3), 2.75-1.50 (m, 13H, AdH).

Anal. Calcd. for $C_{17}H_{20}OS$ (272.41): C, 74.96; H, 7.40. Found: C, 74.45; H, 7.35.

1-(4-Methylthiophenyl)-2-cyanoadamantane: Potassium t-butoxide (20.45 g, 182.2 mmol) was added all at once to a solution of tosylmethyl isocyanide (15.8 g, 80.7 mmol) in DMSO (95 mL) (ice-cooling). The mixture was allowed to stir at ambient temperature for 5 min followed by adding 1-(4-methylthio-

phenyl)-2-adamantanone (7.33 g, 26.9 mmol) in methanol (11 mL). The mixture was allowed to stir at room temperature (1 h) and at 45 ^{o}C (72 h) was cooled and poured into a solution of diluted HCl (100 mL 1 N HCl and 100 mL water) and was extracted with CH_2Cl_2 (3 x 150 mL). The combined CH_2Cl_2 layers were washed with water (5 x 300 mL) and were dried ($MgSO_4$). Solvents were removed, in vacuo. The residue was purified by column chromatography (Alumina F-20), CH_2Cl_2/hexane (1:1) as eluent). The colorless solid (4.47 g, 59%) had mp 84.5-89 ^{o}C. Repeated recrystallization from CH_2Cl_2/hexane gave colorless prisms, mp 90.5-93 ^{o}C; IR (KBr) 2232 cm^{-1} ($C \equiv N$); ^1H NMR ($CDCl_3$) δ 7.27 (s, 4H, Ar), 3.10 (br s, 1H, CHCN), 2.47 (s, 3H, SCH_3), 2.65-1.06 (m, 13H, AdH).

Anal. Calcd. for $C_{18}H_{21}NS$ (283.44): C, 76.28; H, 7.47. Found: C, 76.22; H, 7.54.

[1-(4-Methylthiophenyl)-2-adamantyl]methylamine Hydrochloride: A solution of 1-(4-methylthiophenyl)-2-cyanoadamantane (0.5 g, 1.76 mmol) in THF (15 mL) was added to an ice-cold suspension of $LiAlH_4$ (0.76 g, 20 mmol) in THF (15 mL). The mixture was stirred at ambient temperature (1 h) and then refluxed (30 h). The mixture was cooled and decomposed by adding successively water (0.76 mL), 15% NaOH (0.76 mL), and water (2.28 mL). The mixture was refluxed for 10 min, was cooled, and the white ppte was filtered and washed thoroughly with ether. The filtrate was distilled, in vacuo, and the residue was dissolved in dry ether and dried ($MgSO_4$). The ether solution was filtered, HCl gas was allowed to bubble into the filtrate. The light yellow solid (0.36 g, 63%) was recrystallized from ethanol/ether which gave white granules, mp 316-320 ^{o}C (decomp); IR (KBr) ~3026 cm^{-1} (NH_3^+); ^1H NMR (DMSO) 7.93 (br s, 3H, exchangeable with D_2O, NH_3^+), 7.26 (s, 4H, Ar), 3.45 (br s, 2H, CH_2N), 2.46 (s,

3H, SCH_3), 2.98-0.50 (m, 14H, AdH); MS, m/e 289 [(M^+ + 2), 4.42], 288 [(M^+ + 1), 18.00], 287 (M^+, 60.94), 163 (100), 137 (65).

Anal. Calcd. for $C_{18}H_{26}ClNS$ (323.93): C, 66.74; H, 8.09; N, 4.33. Found: C, 66.48; H, 8.17; N, 4.06.

N-[1-(4-Methylthiophenyl)-2-adamantyl]methyl-2-chloroacetamidine Hydrochloride: Chloroacetonitrile (0.15 g, 2.04 mmol) was added to a solution of sodium methoxide [prepared from sodium (4.6 mg) and dry methanol (2 mL)] and the mixture was allowed to stir at ambient temperature for 1.5 h. A solution of [1-(4-methylthiophenyl)-2-adamantyl]methylamine hydrochloride (0.6 g, 1.85 mmol) in methanol (4 mL) was added and the pH of the solution was adjusted to about 4 by adding methanolic HCl. The mixture was allowed to stir at room temperature overnight. Solvents were removed, in vacuo, and the residue was triturated with petroleum ether. The solid was washed successively with water and ether, and then dried in a dessicator over P_2O_5. The beige solid (0.6 g, 81%) melted between 199-203 ^{o}C (decomp). Recrystallization from ethanol/petroleum ether gave beige prisms, mp 214-216 ^{o}C (decomp); IR (KBr) 1678 ($C{=}NH_2^+$), 1639 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6) δ 9.83, 9.41, 9.02 (three br s, 3H, exchangeable with D_2O, 3NH's), 7.24 (s, 4H, Ar), 4.31 (s, 2H, CH_2Cl), 3.43 (br s, 2H, CH_2N), 2.46 (s, 3H, SCH_3), 3.01-1.18 (m, 14H, AdH).

Anal. Calcd. for $C_{20}H_{30}Cl_2N_2S$: C, 60.14; H, 7.07; N, 7.01. Found: C, 60.23; H, 7.36; N, 6.75.

The solid was washed successively with ether, carbon disulfide, toluene and ether again to weigh 4.51 g. After recrystallization from ethanol/carbon disulfide/ether, a light yellow solid was obtained (3.41 g). Recrystallizaiton from 2-propanol/toluene/ether afforded a white powder, (2.20 g, 42%) mp 201-204 ^{o}C (decomp); ^{1}H NMR (DMSO-d_6/$CDCl_3$/few drops of TFAA to achieve solution) δ 9.31, 9.08, 8.57 (br s, exchangeable NH, OH protons), 7.24 (br s, 4 Ar

H's), 3.59 (d, J = 16.8 Hz, C$\underline{H}_2$-S-P), 2.46 (s, SCH_3); 3.31-60.85 series of multiplets for CH_2N and adamantane protons.

Anal. Calcd. for $C_{20}H_{29}N_2O_3PS_2$ (440.56): C, 54.53; H, 6.63; N, 6.36. Found: C, 54.56; H, 6.65; N, 6.23.

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